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Review of literature: Role of 5-aminolevulinic acid and sleep*

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ABSTRACT

Objective: To determine if current peer-reviewed literature supports the existence of a relationship between the administration of dietary supplements containing 5-Aminolevulinic Acid (5-ALA) and sleep. Methods: Conceptual analysis of a systematically defined group of data is based on publications in referred journals. Constant comparative analyses were used to analyze the data. Detailed analyses were used to identify trends that led to qualifying relationships between the use of 5-ALA and heme. In addition, the relationship among heme, melatonin, and sleep were explored. Since there were no published data related to 5-ALA and sleep, an analysis of what is known about 5-ALA and heme was undertaken. Results: Currently, within the scope of this review, no literature available directly connecting 5-ALA and sleep was found. Research indicates that 5-ALA has an indirect relationship with intra-cellular energy production, which could result in a wide range of effects from cellular to endocrine to neurologic to behavioral. In addition, there is evidence that 5-ALA may influence tryptophan and serotonin levels. Conclusion: While there are no studies on 5-ALA and sleep were found, current research suggests several potential mechanisms by which 5-ALA could influence sleep. The mechanisms suggest the potential for 5-ALA to assist in the adjustment of a person's circadian cycle, endocrine function, or neurologic function in order to allow for better sleep in a natural way. In doing so, it may provide for a safer alternative to currently available sleep medication. Further research is needed to explore this possibility.

Keywords: Insomnia; Heme; Melatonin; Energy; Metabolism; 5-Aminolevulinic Acid; Sleep

1. INTRODUCTION

Insomnia is a serious health problem that affects millions of people. Sleep and wakefulness disorders are estimated to impact about 50 - 70 million adults in the United States [1]. More than half of the people report difficulties in sleeping indicate that the problem is "occasional", or around 6 nights per month [2]. Nearly one quarter of people with sleep disorders report frequent or chronic insomnia [2]. They experience problems about 16 nights per month [2]. Often those with insomnia describe experiencing both difficulty in falling asleep and wakefulness during sleep [2].

Insomnia prevalence in the general population is estimated at 30% - 50% [3]. Medications currently used to treat sleep disorders have negative side effects. In addition, all sleep medications cause drowsiness. Remarkable improvement in sleep was reported by several participants in a previously conducted study investigating the relationship between the dietary supplement 5-ALA and pre-diabetes. The dietary supplement 5-ALA could potentially be an alternative approach to improving sleep. 5-ALA creates energy and may adjust a person's circadian cycle in order to allow for better sleep in a natural way. The purpose of this investigation is to analyze what has been published in peer-reviewed journals about 5-ALA and sleep.

Sleep and 5-ALA

In a previous study conducted to examine the relationship between 5-ALA and pre-diabetes, a questionnaire covering a wide range of measures of health was administered. A daily diary asking participants how they felt was completed throughout the study. The study placed

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participants on the 5-ALA supplement for a period of 12 weeks. The participants were surveyed with a questionnaire at Week 0 and Week 12, interviewed, and their daily diary reviewed at Weeks 0, 4, 8, 12, and 16. In the course of this study, some interesting results relating to sleep patterns emerged. From the 154 participants in this study, one of the blinded physicians wrote to 2 case reports on selected participants. The data from the case reports suggest that 5-ALA may be related to improved sleep. The report indicated that sleep patterns improved while on the 50 mg supplement, and then returned to previous patterns when the supplement was stopped. This evidence provided a strong rationale to support this investigation.

2. STATE OF THE SCIENCE

5-ALA is known to be a basic building block of heme production. The porphyrin synthesis pathway that leads to heme production in mammals is composed of several compounds and 5 ALA is the first.

Heme plays a role in cellular energy transport system [4]. Cellular energy generation uses membrane-localized electron transfer chains for adenosine-5'-triphosphate (ATP) synthesis [4]. ATP uses the cells to transport chemical energy for metabolism [4]. Understanding the relationship between 5-ALA and heme production might provide evidence that explains why 5-ALA may or may not have a relationship with sleep.

3. METHODS OF THE SEARCH PROCESS

The review of literature in this paper was based on conceptual analysis of a systematically defined group of data published in referred journals using Grounded Theory Methods. Constant comparative analyses were used to direct the analysis. This analytic technique developed by Glasser and Strauss is used to investigate human phenomena and explain behavior and experience. It is an appropriate method to explore studies related to sleep [5]. The theoretical underpinnings of grounded theory sociological theories of symbolic interaction [5]. Methods associates with this theory in clued constant comparative analysis where data is analyzed by comparing it with the other data after each unit selected for analysis has been coded. Themes are then generated and developed in to constructs or themes that describe possible relationships within the data [5]. The database used for this review was PubMed. The search terms used initially in the investigation included: 5-ALA and sleep.

***Inclusion Criteria*:** Specific Terms included-Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Disorder (DSPD), Advanced Sleep Phase Disorder (ASPD), Shift Work Disorder, Irregular Sleep-Wake Type, Insomnia, Heme, Melatonin, Energy, 5-ALA, and Metabolism.

***Exclusion Criteria*:** Specific Terms included-Primary Hypersomnia/Narcolepsy without Cataplexy, Narcolepsy/Hypocretin Deficiency, Obstructive Sleep Apnea, Hypopnea Syndrome, Primary Central Sleep Apnea, Primary Alveolar Hypoventilation, Disorder of Arousal, Nightmare Disorder, Free-Running, Jet-Lag, Rapid Eye Movement, Behavior Disorder, Restless Leg Syndrome, Other Specified Sleep Disorder, Unspecified Sleep Disorder, and all other dietary supplements used to treat sleep disorders.

No data based literature emerged, thus the terms insomnia, heme, melatonin, energy and metabolism were explored. Snowballing was also implemented. A total of 133 English language papers published between 2007 and 2012 were included in this search. These papers were entered into a matrix and themes generated. The themes were organized and categorized and are reported in the results section. Only data based clinical trials and review articles were included. Hypotheses were then formulated using the themes generated during the analysis. This investigational process is the expected outcome from Grounded Theory Methods.

4. FINDINGS OF THE ANALYSIS INCLUDING PLAUSIBLE PATHWAYS

The following themes emerged during the analysis: 5-ALA Production and Interactions, Brief History of 5-ALA, Melatonin and 5-ALA and Heme. Each of these themes is summarized in-depth below.

4.1. 5-ALA Production and Interactions

Five-ALA can be found in many common foods, such as spinach, tomatoes, shitake mushrooms, potatoes, squid, ground beef, wine and soy sauce. The normal intake from food containing 5-ALA is 1 - 2 mg/day. Five-ALA is synthesized by the body at a rate of 600 mg/day [6]. It is believed that after 40 years of age the body begins to produce about 550 mg/day [6].

5-ALA is a natural amino acid, the precursor of chlorophyll and heme [5]. Eight molecules of 5-ALA make porphyrin. A porphyrin has many double bonds and nitrogen's lone pair of electrons. In the presence of levulinic acid some photosynthetic bacteria, can produce ALA under light [7]. Decreased heme enzyme activity causes a decline in the mitochondrial electron transfer system, which decreases consumption of glucose [8]. Glucose intolerance which leads to type 2 diabetes is currently thought to begin with lipid accumulation which induces adipocytokines to decrease insulin sensitivity in cells [6]. This causes an increase in the blood sugar level which in turn causes glycoproteins to accumulate in the blood vessels [6]. In addition, insufficient production of

cytochrome causes a decline in the mitochondria electron transfer system; that is, it lowers the basal metabolism [6]. Animal research has shown that administration of 5-ALA can directly enhance aerobic energy metabolism [9].

4.2. Brief History of 5-ALA

Five-ALA is a dietary supplement. It is produced in plants and animals differently. Chlorophyll synthesis is regulated in plants partially by 5-ALA. If a plant is provided with 5-ALA toxic levels of the chlorophyll precursor, protochlorophyllide can develop. This illustrates the synthesis of this intermediate protochlorophyllide and it is not suppressed downwards in the chain reaction [10]. Protochlorophyllide is a strong photosensitizer in plants [10]. "It is produced by the enzyme ALA synthase, from glycine and succinyl CoA" [10]. This process is called the Shemin pathway [10].

In plants, 5-ALA is produced from glutamic acid via glutamyl-tRNA and glutamate-1-semialdehyde [4,11]. "The enzymes involved in this pathway are glutamyl-tRNA synthetase, glutamyl-tRNA reductase and glutamate-1-semialdehyde aminotransferase" [2,9]. This process is known as the C5 or Beale pathway [4,11].

Five-ALA has been shown to synthesize and assist with the build-up of fluorescent porphyrins (protoporphyrin IX) in epithelia and neoplastic tissues, often malignant gliomas [12]. There are a number of investigations where it has been used to visualize cancerous masses [12]. Intra-operative use of this method may reduce the tumor volume and prolong survival [12]. 5-ALA has also been used as a photosensitizer.

4.3. Melatonin

Melatonin is a chemical that occurs naturally [13]. The concentration varies in a daily cycle, and is higher during the hours of sleep, and lower during wakefulness [13]. Melatonin allows a person to become sleepy. Extended or enhanced day-phase activity can result in increased melatonin in the evening. "Melatonin is a hormone produced by the pineal gland that contributes to the reinforcement of circadian and seasonal rhythms" [14]. 5-ALA may, in fact, enhance day-phase activity, which could indirectly increase the natural production of hormonal production of melatonin in the evening.

During phase-advance, or during the night when sleeping, the body uses its naturally produced melatonin. The numbers on the circadian clock represent a period slightly greater than a 24-hour cycle. Circadian time is displayed in **Figure 1**. From left to right, it represents morning, afternoon, evening, and night. Zero (0) is bedtime and 8 is the end of the sleep cycle. The graph in depicts the average light a person experiences in one day. The human body produces endogenous melatonin, provided the lighting is dim about two hours before bedtime. This process if called dim-light melatonin onset, DLMO [15]. DLMO assists with regulation of the sleep-wake schedule [16].

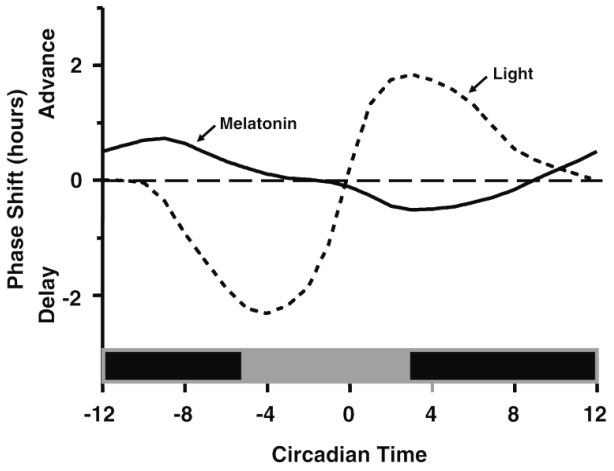

Figure 1. Schematic representation of the phase response curves to light and melatonin. Circadian time point 0 reflects the temperature nadir. Light exposure prior to the temperature nadir results in a delay of circadian rhythms, whereas light exposure after the temperature nadir causes phase advances. Note that there is a dead zone in the middle of the day where bright light exposure has no effect on the timing of circadian rhythms. In contrast, melatonin administered in the beginning of the night advances the circadian rhythm, while melatonin in the morning delays the circadian rhythm. Adapted from Lewy *et al*. [24], Khalsa *et al*. [25] and Zee *et al*. [26] with permission.

4.4. 5-ALA and Heme

What is the relationship between 5-ALA and heme production? As glucose levels increase in cells, the human body's ability to produce 5-ALA is reduced. In addition, 5-ALA production decreases in the human body at or around the age of 40, at a rate of 50 mg per day [4]. When heme enzyme activity decrease, hemoglobin production will be reduced. A decline in the mitochondrial electron transfer system follows, with decreased basal metabolism as well as physical energy decline and possibly depression [4]. Since the day shift phase contributes to melatonin production, and melatonin allows a person to be sleepy, extended or enhanced day-phase activity could result in increased melatonin production during the evening. Therefore, 5-ALA could, in fact, enhance day-phase activity, which could inversely allow a person to experience a better sleep cycle.

4.5. Sleep

"Circadian Rhythm Sleep Disorders all involve a problem in the timing of the sleep and is wakefulness cycle" [17]. A master circadian clock in the brain called the su-

prachiasmatic nucleus (SCN), controls the timing of body rhythms related to temperature and hormone levels over a cycle that lasts a little longer than 24 hours [17].

4.6. Sleep Disorders

Sleep Insomnia, as defined by the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders DSM-5 Sleep Disorders (the planned fifth edition), is defined within the following three durations: acute insomnia, less than 1 month, sub acute insomnia occurs every 1 to 3 months, and persistent insomnia occurs 3 months or more [18]. Insomnia is defined by an individual's report of sleeping difficulties. [19]. Insomnia can be defined as affirmation of difficulty sleeping or difficulty falling or staying asleep (polysomnographic evidence of disturbed sleep) [19].

Insomnia is often difficult to diagnose, as it may be related to other environmental factors. In the following section, a number of sleep disorders that may be reported as insomnia and might have a relationship with 5-ALA and heme are described. From the research of R.L. Sack, et al, the American Academy of Sleep Medicine (AASM) has cited the following as sleep disorders: Delayed Sleep Phase Disorder (DSPD), Advanced Sleep Phase Disorder (ASPD), Shift Work Disorder, and Irregular Sleep-Wake Rhythm.

DSPD is a circadian rhythm sleep disorder. It is chronic problem related to the "timing of sleep, the peak period of alertness, the core body temperature rhythm, hormonal and other daily rhythms" [17]. Those who experience DSPD fall asleep after midnight and have significant difficulty waking up in the morning [17]. "Individuals with DSPD phase type are more alert in the evening and early nighttime, stay up later, and are very tired in the morning" [17]. Those that suffer from DSPD cannot sleep until early morning. Yet, they fall asleep at about the same time each evening. This can compromise their ability to get to work or school on time. If 5-ALA can improve the circadian cycle during the day, people with DSDP may be able to naturally adjust to a normal schedule and experience normal sleep.

Dr. Elliot D. Weitzman and others at Montefiore Medical Center were the initial investigators to identify DSPD [2]. DSPD can be severe and inflexible; it is an invisible disability [14]. ASPD a circadian rhythm sleep disorder is also known as advanced sleep phase syndrome (ASPS). This syndrome is associated with feeling very sleepy and a need to go to bed early (eg, 6:00 - 8:00 p.m.). Those afflicted with this problem wake early in the morning (eg, around 3:00 a.m.) and have trouble returning to sleep. They find themselves unable to stay awake until it is time to go to bed and unable to stay awake during the day. Those with this problem have Melatonin levels and core body temperature levels that cycle a number of hours earlier than the majority of the population [2].

If 5-ALA can increase day phase activity which could indirectly increase melatonin production, it is possible that 5-ALA could cause a person with ASPD to experience a longer day and experience a normal sleeping cycle after a specified period of time. It is unknown what this time period is, and further research would be necessary in order to determine this possibility for this disorder.

Shift Work Disorder occurs when a person's work shift occurs during normal sleeping hours. The person feels sleepy during the night shift and awake during the day. According to this review, circadian rhythm is the internal timing system that humans have adapted in a 24-hour cycle. The SCN located in the anterior hypothalamus is the body's generator of the circadian rhythms. The SCN regulates the circadian rhythms on a molecular level. This cycle controls sleep and wakefulness. In order for this system to function efficiently, it needs information from a variety of sources, which include physical activity, social activities and to experience day and night. The ganglion cells in the retina collect light information for the SCN. These cells produce a pigment called melanopsin and are particularly sensitive to light; they also comprise the pathway for rod and cone signals to the brain [20]. This is true for "non-image visual functions, such as circadian photo-entrainment and the pupillary light reflex" [20]. Light exposure is needed by the pineal gland to produce melatonin and is regulated by the SCN. Melatonin taken as a dietary supplement in the in the evening or at any other time during the day can phase-advance the sleep-wake rhythms [13]. In addition when melatonin supplements are taken in the morning they will phase-delay circadian rhythms [13]. Shift Work Disorder may be better treated with melatonin. It is unlikely that 5-ALA would have any effect on a person experiencing Shift Work Disorder, since regular day awake time is necessary for the SNC to collect light which is needed to produce melatonin.

Irregular Sleep-Wake Rhythm can be defined as a situation during which the patient has an undefined sleep-wake cycle and the patients sleep patterns continue to occur on an irregular basis during a 24-hour period [18]. Often this pattern occurs in adults with dementia and children with mental retardation suggesting an association with cerebral damage or degeneration or brain structure abnormalities [18]. It is possible that 5-ALA could restore an Irregular Sleep-Wake Rhythm over an unspecified period of time. Further research would be necessary to make this determination accurately.

4.7. Treatment of Sleep Disorders

Medications used to treat sleep disorders have negative

side effects. For this reason, there is a great interest in natural alternatives such as 5-ALA for the treatment of sleep disorders. According to S. W. Lockley, "many aspects of human physiology and behavior are dominated by 24-hour rhythms that have a major impact on our health and well-being" [21]. Knowing that 5-ALA plays a role in energy production, it is possible to conclude that a person who experiences a longer day-shift will spend more time in the light-phase and thereby produce additional melatonin when entering the night-phase, and will be able to experience a continuous sleep at regular intervals.

5. DISCUSSION AND SUMMARY HYPOTHESIS

The themes that emerged during this analysis reveal that current research supports several possible mechanisms for the improvement of sleep. 5-ALA as a key component of heme and the cytochrome system appears to have an impact on increasing the energy of all cells. Research on ATP and cytochrome C oxidase activity in mice in relation to 5-ALA suggest this to be true [9]. One possibility may be that 5-ALA helps each cell's metabolism, in a way that better defines a person's circadian rhythms. From an endocrine perspective, increased energy may help all endocrine organs function optimally and induce better sleep through better hormonal function. One may also speculate that 5-ALA may support an increase in the individual's day-phase activity, and contribute to hormonal regulation, including melatonin production in the pineal gland. This may result in better sleep and corticosteroid production in the adrenal glands. Another possible mechanism is through 5-ALA's apparent influence on tryptophan and serotonin, which are substances known to have a role in sleep. In research involving test mice, researchers found that the regular administration of 5-ALA appeared to raise serotonin levels in the brain [22]. Remarkably, similar research found that 5-ALA was associated with an increase in tryptophan and serotonin in the forebrain during the night and a decrease during the day [23].

This is potentially very important because it may make for an ideal sleep-aid that assists in inducing drowsiness at night and wakefulness during the day and minimizes the unwanted side effects related to drowsiness. It should be noted that this particular research did not find any change in melatonin levels in the pineal gland, however.

Although these studies suggest an effect on brain function, no studies on the effect of 5-ALA and brain or neurologic function were found. The effect of 5-ALA on ATP levels, cytochrome C oxidase in general, and on serotonin levels in the forebrain suggest that there may be an effect on EEG patterns that may elucidate its potential effect on sleep.

These various findings supported by the preliminary data from previous investigations strongly suggest the need for additional research. Studies to evaluate the hypothesis regarding the clinical significance of the use of 5-ALA and a relationship with sleep are needed.

6. CONCLUSION AND RECOMMENDATIONS

Currently, within the scope of this review, no literature available directly connecting 5-ALA and sleep was found. What current research indicates about 5-ALA and sleep is that 5-ALA has an indirect relationship with intracellular energy production and an effect on potentially neuroactive substances such as tryptophan, serotonin, or melatonin. Enhanced cellular energy production could result in a wide range of effects from cellular to endocrine to neurologic. In addition, animal studies indicate a possible effect on neurotransmitters which may have an effect on the sleep-wake cycle. Medications currently used to treat sleep disorders induce drowsiness and have negative and even fatal side effect. In addition, many sleep medications induce a tolerance and are recommended only for short-term use. 5-ALA may assist in the adjustment of a person's circadian cycle, endocrine function or neurologic function in order to allow for better sleep in a natural way. In doing so, it may provide for a safer alternative to currently available sleep medication. Further research is needed to explore this possibility.

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