

-  Lais Marins¹
 Mariana Franchini¹
 Jessica Fabia Polese²
 Valdete Guandalini¹
 Juliana Barbosa Coltinho³
 Maria Teresa Martins Araújo³

¹Universidade Federal do Espírito Santo, Centro de Ciências da Saúde, Departamento de Educação Integrada em Saúde. Vitória, ES, Brasil.

²Universidade Federal do Espírito Santo, Hospital Universitário "Cassiano Antônio Moraes". Vitória, ES, Brasil.

³Universidade Federal do Espírito Santo, Centro de Ciências da Saúde, Departamento de Ciências Fisiológicas. Vitória, ES, Brasil.

Correspondence

Maria Teresa Martins Araújo
marajujo.27@hotmail.com

Tryptophan-rich diet can influence sleep quality in different phases of life

Dieta rica em triptofano pode influenciar a qualidade do sono em diferentes fases da vida

Abstract

Objective: To evaluate how the ingestion of tryptophan (food sources and supplementation) influences the circadian rhythm and sleep quality of humans and animals from different age groups. **Methods:** This is an integrative review of the literature conducted in PubMed and Capes Journals Portals, considering the period between 1998 and 2020 in Portuguese, English or Spanish languages. The guiding question was: "Does the intake of tryptophan through food sources and supplementation interfere with the circadian rhythm and quality of sleep?". The following inclusion criteria were used: analysis of the descriptors ("tryptophan", "diet", "sleep") in the title or abstract of the article; contextualization of the guiding question in the whole article; type of article and sample studied in the article. At the end, 12 articles were included in the study, eight of those having been carried out in humans and four in animals. **Results:** All 12 studies showed that, when a daytime and/or nighttime tryptophan-rich diet, whether from dietary sources or supplementation, is administered to children (n = 2), adults (n = 6), adult animals (n = 2) and young and old animals (n = 2), a significant contribution to the synthesis of serotonin and melatonin took place. The presence of these mediators changed the chronobiology of the sleep-wake cycle, interfering with the quality of sleep of humans and animals. **Conclusion:** Foods that affect the availability of tryptophan – or its supplementation – and the synthesis of serotonin and melatonin were able to organize the sleep of newborns and improve sleep for adults and the elderly, regardless of the period of the day. Thus, proposals for chronobiologically formulated diets with tryptophan may contribute to low-cost therapeutic approaches that would circumvent or reduce sleep disorders.

Keywords: Diet. Dietary Supplements. Tryptophan. Circadian rhythm. Sleep.

Resumo

Objetivo: Avaliar como a ingestão de triptofano (fontes alimentares e suplementação) influencia o ritmo circadiano e a qualidade do sono de humanos e animais em diferentes faixas etárias. **Métodos:** Trata-se de uma revisão integrativa da literatura realizada nos Portais de Periódicos PubMed e Capes, considerados no período de 1998 a 2020 nas línguas portuguesa, inglesa e espanhola. A questão norteadora foi: "A ingestão de triptofano através de fontes alimentares e suplementação interfere no ritmo circadiano e na qualidade do sono?". Os seguintes critérios de inclusão foram utilizados: análise dos descritores ("tryptophan", "diet", "sleep") no título ou resumo do artigo, contextualização da questão norteadora em todo o artigo, tipo de artigo e amostra estudada no artigo. Ao final, 12 artigos foram incluídos no estudo, sendo oito estudos realizados em humanos e quatro em animais. **Resultados:** Os 12 estudos mostraram que quando a dieta diurna e/ou noturna rica em triptofano, seja por fontes

alimentares ou suplementação, é administrada em crianças (n=2), em adultos (n=6), em animais adultos (n=2) e animais jovens e velhos (n=2), houve significativa contribuição para a síntese de serotonina e melatonina. A presença desses mediadores alterou a cronobiologia do ciclo vigília-sono, interferindo na qualidade do sono de humanos e animais.

Conclusão: Alimentos que afetam a disponibilidade de triptofano ou sua suplementação e a síntese de serotonina e melatonina foram capazes de organizar o sono dos recém-nascidos, melhorar o sono de adultos e idosos, independentemente dos períodos do dia. Assim, propostas de dietas cronobiologicamente formuladas com triptofano poderiam contribuir para abordagens terapêuticas de baixo custo que contornariam ou reduziriam os distúrbios do sono.

Palavras-chave: Dieta. Suplementos Nutricionais. Triptofano. Ritmo circadiano. Sono.

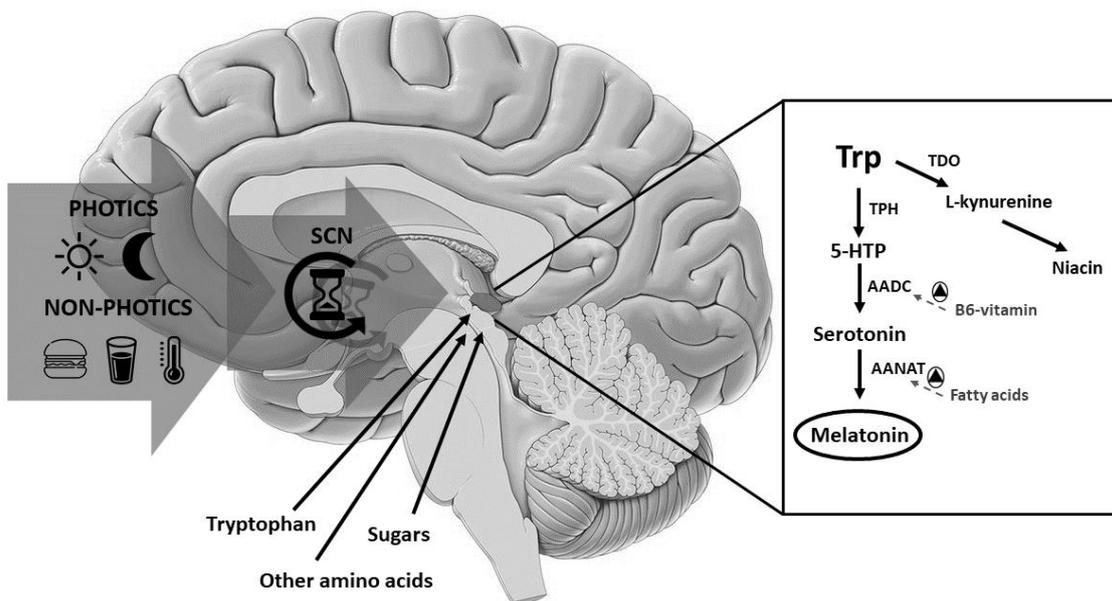
INTRODUCTION

Several studies have associated sleep with the incidence of chronic diseases such as obesity, hypertension and type 2 diabetes mellitus.¹ On the other hand, the consumption of foods such as milk, fresh fruits, vegetables, whole grains, sources of low-fat protein, B-complex vitamins, minerals and unrefined carbohydrates has been related to sleep quality.² Among these foods, those that affect tryptophan availability and the synthesis of serotonin and melatonin may interfere with the sleep-wake cycle.²

When the tryptophan concentration in the bloodstream rises, its passage through the blood-brain barrier is facilitated, and, in the brain, this amino acid is metabolized following two main pathways: the kynurenine pathway and the 5-hydroxytryptophan pathway (figure 1).

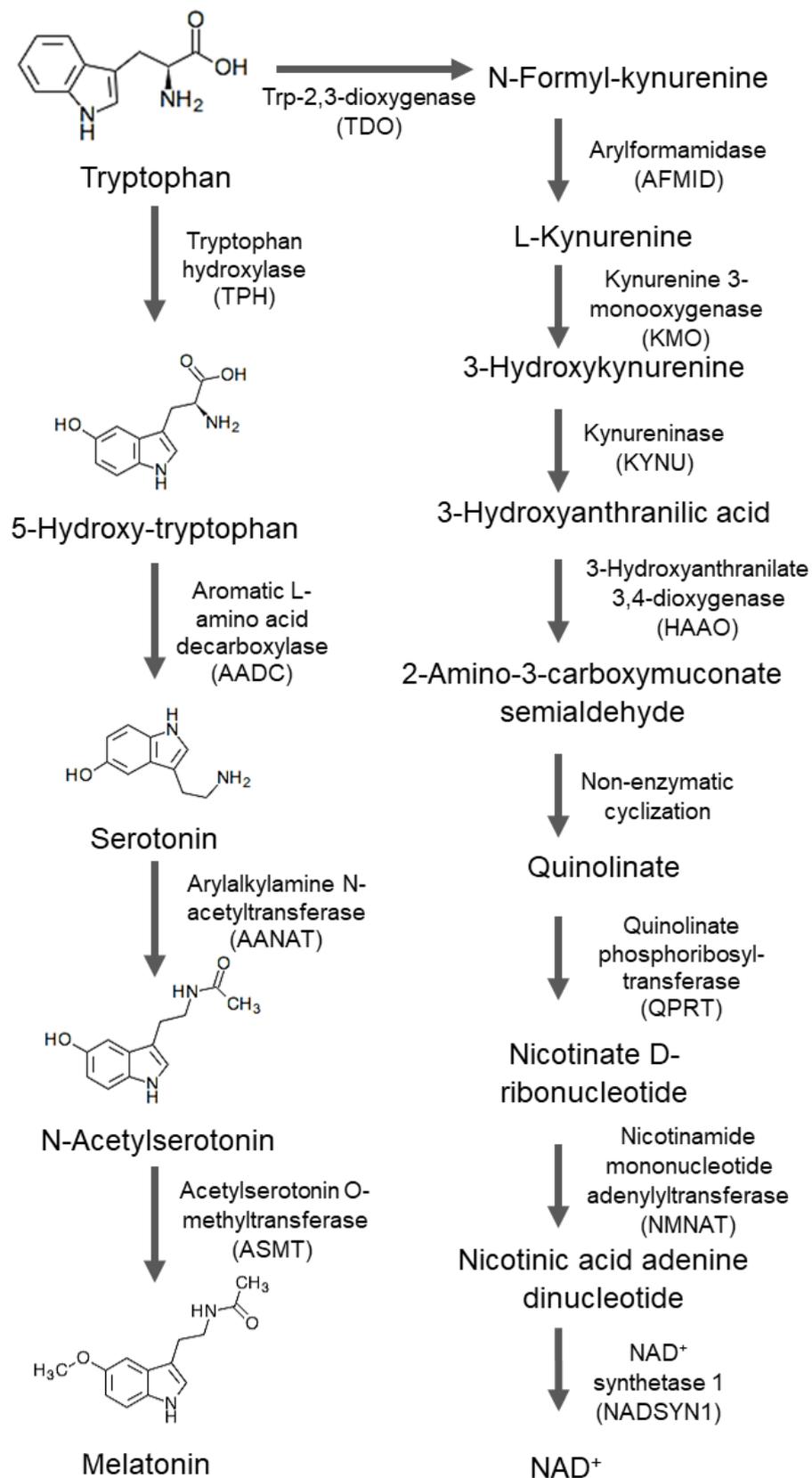
The enzyme tryptophan-2,3-dioxygenase (TDO) catalyzes the first step of the kynurenin pathway (figure 2), where tryptophan is converted to niacin (vitamin B3).^{2,3} Niacin, in turn, suppresses TDO activity,² prioritizing the pathway of 5-hydroxytryptophan formation (figures 1 and 2). In this pathway, tryptophan is converted to serotonin, which, through a fatty acids-dependent enzymatic process,^{2,3} is converted into melatonin in the pineal gland⁴ and also in other brain regions such as the hypothalamus, hippocampus, cerebellum and striatum.^{2,5}

Figure 1. Mechanisms by which dietary components influence the synthesis of serotonin and melatonin as evidenced by the literature available in PubMed and Capes Journals Portals, between 1998 and 2018. The tryptophan-2,3-dioxygenase (TDO) enzyme catalyzes the first step of the kynurenine pathway where tryptophan is converted into niacin (B3-vitamin). Niacin suppresses TDO activity, prioritizing the pathway in which the tryptophan hydroxylase (TPH) converts tryptophan into 5-hydroxy-tryptophan which is metabolized in serotonin, by an enzymatic process dependent on fatty acids, and then, serotonin is converted in melatonin in the pineal gland.



Subtitle: SCN: suprachiasmatic nucleus; Trp: tryptophan; 5-HTP: 5- hydroxytryptophan; TDO: tryptophan-2,3-dioxygenase; TPH: tryptophan hydroxylase; AADC: aromatic L-amino acid decarboxylase; AANAT: arylalkylamine-N-acetyltransferase. Source: the authors, based on the study data Peuhkuri et al.²

Figure 2. Biosynthesis pathways of melatonin and niacin from tryptophan in humans.



Source: the authors, based on KEGG database resource.⁵

As the circadian rhythm is continually redefined by signals that can be classified as either photic or non-photic on the pacemaker of the Supra-Chiasmatic Nucleus (NSC) (figure 1), there could be a connection between the circadian timing system and metabolism.⁶⁻⁸

Feeding is a non-photic synchronizer of the NSC, thus there is a connection between the circadian timing system and the metabolism.⁹ Based on the concept of chrono-nutrition, the circadian rhythm of wakefulness/sleep can still be influenced by the time of day when food was ingested.¹⁰ The metabolic responses related to food intake (even when the same meal is ingested) are influenced by the circadian rhythm, which means these responses are different depending on the moment each meal was taken. Thus, an ideal time-restricted diet could prevent, for example, metabolic disorders.¹¹

However, although the circadian rhythm and melatonin production are well marked in young organisms, neither are fully functional in infants^{12,13} nor in the elderly.¹⁴ Based on the premise that some dietary components – especially tryptophan – influence sleep chronology, chronobiology and chrono-nutrition, they have become useful tools for understanding the interference of neurohormonal mediators in sleep efficiency in the various phases of the patients' lives – newborns to the elderly. This may be evidenced in studies that demonstrate a significant improvement in sleep or sleep-wake rhythm in people and animals from different age groups, who were fed a protein diet associated or not with the administration of formulations enriched with tryptophan or melatonin at different times.¹⁴⁻¹⁶ Thus, this integrative review aimed to evaluate how the intake of tryptophan, through food sources and supplementation, influences the circadian rhythm and sleep quality of humans and animals from different age groups.

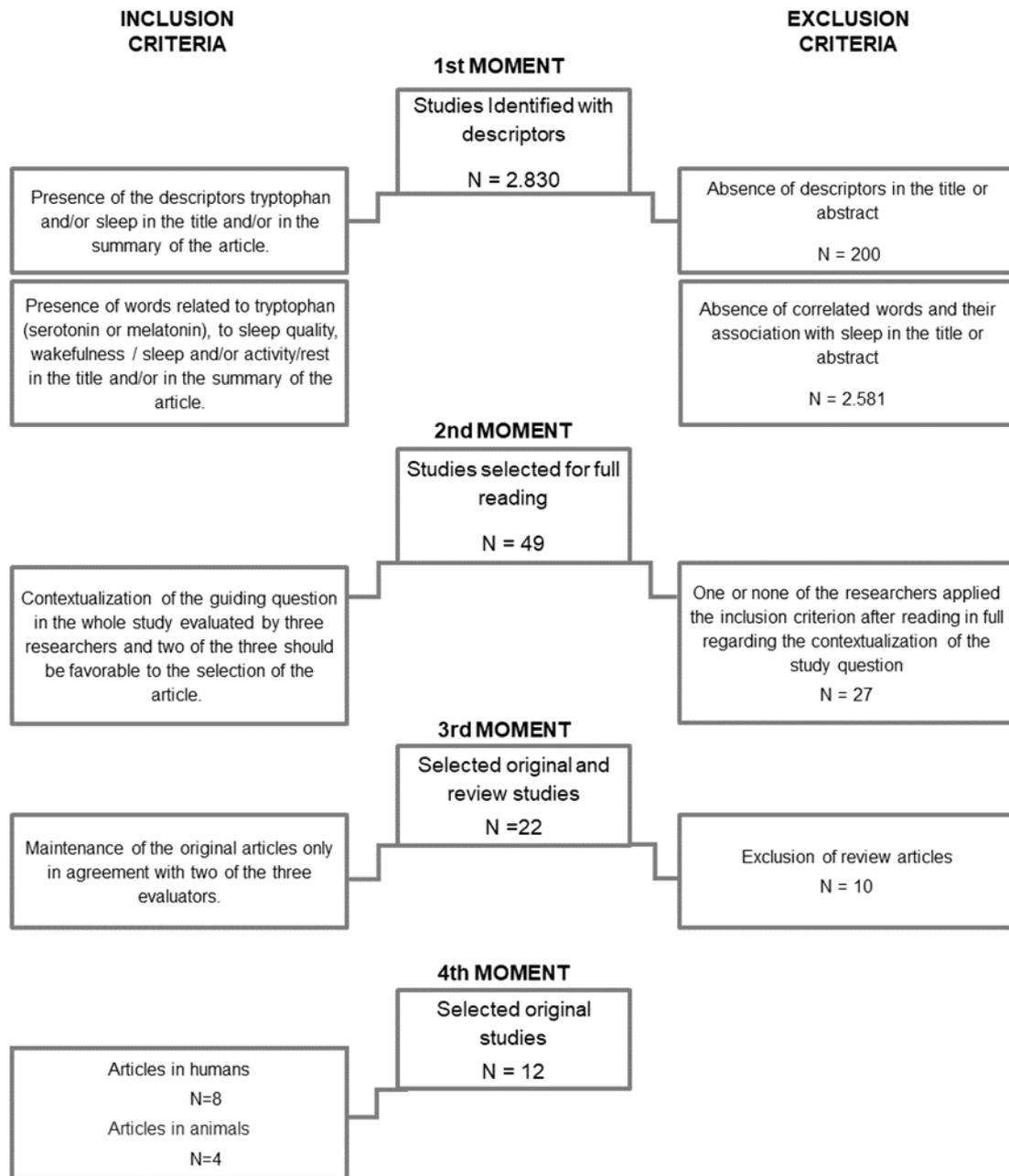
METHODS

This study is a literature review in which the analysis and synthesis of the results were established by the following guiding question: Does tryptophan intake, through food sources and supplementation, interfere with circadian rhythm and sleep quality?

Firstly, the review covered the period between 2018 and 2020 and consisted in the selection of scientific articles published between January 1998 and June 2018 in Portuguese, English or Spanish, through an electronic search in the PubMed database and the Capes Journals Portal. The following descriptors were used to survey the topic: "tryptophan" "sleep" "diet", in combination with the Boolean operator AND.

Secondly, the analysis of the selected articles was based on inclusion and exclusion criteria that encompassed four points: 1st - Analysis of the descriptors in the title and in the abstract of the article; 2nd - Contextualization of the guiding question in the article as a whole; 3rd - Evaluation of the type of study and 4th - Division of studies (human and/or animals). To minimize errors or omission, the articles were independently selected by two researchers to begin with, being then evaluated by a third party. Thus, of the 2,830 articles found through the electronic search, 49 were deemed suitable for the analysis. Of the 22 articles that remained following a further selection, 10 were excluded for being review articles. Of the 12 articles that remained in the study, 8 were conducted in humans and 4 in animals (figure 3). All selected articles were published in indexed, peer-reviewed journals with high impact factors (average value of 4.09).

Figure 3. Flowchart of the selection process for the review of the literature on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and Capes Journals Portal, between 1998 and 2020.



Source: the authors, based on the study process.

Finally, the 12 selected articles went through yet another form of analysis and synthesis so that the data could be extracted. It consisted in identifying the purpose of each study, the type of population and age of the group studied, the strategy used in the clinical trial (interventions and duration of the study) and the results obtained.

The results of this integrative review are described in two separate charts, one for human studies (Chart 1) and one for animals (Chart 2).

Chart 1. Characteristics of articles that used human - infants, adults, and the elderly analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and the Capes Journals Portal, between 1998 and 2018.

Part A: Articles with human				
Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Voderholzer et al., 1998. ¹⁹ Germany	To analyze the acute polysomnographic effects of tryptophan depletion and induce similar changes in sleep EEG as observed in depressed patients.	12 healthy volunteers. Age: 36 ± 11 years old (six men) and 32 ± 8 years old (six women).	<p>Analysis of Tryptophan: <u>From the 3rd day until the middle of the day of the 4th day:</u> diet with low protein (160mg of tryptophan, 18.6g of protein). <u>Fourth day at 6 pm:</u> A mixture of amino acids devoid of tryptophan (<u>tryptophan depletion</u>) or containing 2.3 g of tryptophan (<u>placebo depletion</u>).</p> <p>Sleep evaluation: Polysomnography for 4 days: 1st day - adaptation; 2nd day - sleep control; 3rd and 4th days - associated with tryptophan depletion in the diet or placebo depletion.</p> <p>Biochemical analyzes: Analysis of free tryptophan levels in plasma by HPLC.</p>	<p>In relation to tryptophan: In the tryptophan depletion this amino acid decreased by 85% while in the placental depletion this increased by 144%.</p> <p>In relation to sleep: After depletion of tryptophan, but not in placebo depletion, there was a decrease in non-REM sleep, stage 2, increased arousal and rapid eye movement (REM) compared to the baseline sleep EEG. REM latency was not altered, however, the first and second intervals of the REM period were significantly lower after tryptophan depletion.</p>

Chart 1. Characteristics of articles that used human - infants, adults, and the elderly analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and the Capes Journals Portal, between 1998 and 2018. (Continues)

Part A: Articles with human				
Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Arnulf et al., 2002. ⁷ France	To evaluate the effects of a rapid tryptophan deficiency in the middle of the morning on sleep the following night.	18 healthy students: 11 women and 7 men Age: 18-38 years (mean: 26 ± 5.9 years).	<p>Analysis of Tryptophan: <u>Two first days:</u> diet with low tryptophan content at home. <u>Third day:</u> administration (double-blind) of tryptophan-free amino acids or placebo in the morning. In the middle of the afternoon intake of food with low tryptophan content until 9pm. <u>Fourth day:</u> at 9:30am a rich tryptophan breakfast was offered. <u>For another 7 days:</u> the procedure established on the third day was repeated.</p> <p>Sleep evaluation: Polysomnography: onset of registration on the third day at 11pm and end of registration on the fourth day at 7:30pm</p> <p>Biochemical analyzes: Analysis of plasma tryptophan on the third day (fasted, until mid-afternoon and night) by HPLC and Analysis of daytime and nighttime concentrations of 6-sulphatoxymelatonin (6-SM) in the urine at the beginning on the third day (at night) and on the fourth day (9h).</p>	<p>In relation to tryptophan: There was a 77% reduction in plasma tryptophan 5 h after ingestion of tryptophan-free amino acids, but after 11 h the tryptophan concentration increased 41% from the baseline.</p> <p>In relation to sleep: Sleep fragmentation increased by 58%. The arousals per hour / sleep during the placebo period was 4.2 ± 0.4 and rose to 6.3 ± 0.9 during rapid depletion of tryptophan. The latency of REM sleep was greater during rapid depletion of tryptophan than during the placebo period, with an average difference of 26 minutes. Stages 1-2 of non-REM sleep during the placebo period were 29 ± 4 min vs 49 ± 9min during rapid depletion of tryptophan. The density of REM was increased during rapid depletion of tryptophan (12.3 ± 2.1%) compared to the placebo period (8.5 ± 1.5%).</p> <p>In relation to biochemical data: Excretion levels of 6- sulphatoxymelatonin at night increased compared to the day, being 5.2 ± 1 µg during the day and 20.2 ± 3.3 µg overnight in the placebo period and during rapid depletion of tryptophan, these were 5.9 ± 0.8 µg during the day and 16 ± 1.2 µg during the night.</p>

Chart 1. Characteristics of articles that used human - infants, adults, and the elderly analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and the Capes Journals Portal, between 1998 and 2018. (Continues)

Part A: Articles with human				
Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Markus et al., 2005. ¹⁸ Netherlands	To assess whether nocturnal consumption of tryptophan-enriched lactoalbumin increases the tryptophan ratio in plasma and the sum of other neutral amino acids (Trp / LNAA) and improves alertness and morning-after-sleep performance in subjects with sleep complaints.	<p><u>Initial sample:</u> 235 students using the questionnaire. After analysis of the highest quartile (good sleepers) and the lowest quartile (poor sleepers) of the questionnaire score, the final sample of 28 students</p> <p><u>Final sample:</u> 14 participants (7 males and 7 females from the "bad sleepers" group) aged 22 ± 2 years and 14 participants (7 men and 7 women in the "good sleepers" group) aged 22 ± 3 years.</p>	<p>Analysis of Tryptophan: Isoenergetic diet (standard): with 325 kcal (13% protein, 86% carbohydrate and 1% fat). Experimental diet (standard + milk shake): milk shake plus other sources of protein (20 g of tryptophan-enriched α-Lactoalbumin (α-LAC) protein (4.8 g / 100 g tryptophan) Placebo (standard + milk shake): milk shake with 20g (1.4g / 100g tryptophan) and sodium caseinate</p> <p>Assessment of sleep / drowsiness / attention: Two nights in the lab to evaluate: behavioral performance, attention during a task of continuous performance (through cerebral measures (potential related to the cerebral event (ERP)) through EEG and drowsiness.</p> <p>Biochemical analyzes: Analysis of LNAA by HPLC.</p>	<p>In relation to tryptophan: There was a significant increase of 130% in the Trp / LNAA ratio 2 h after nocturnal ingestion of a standard diet enriched with α-LAC.</p> <p>In relation to sleep / drowsiness / attention: Subjects had less sleep in the morning after nocturnal ingestion of α-LAC than after placebo intake. Drowsiness reduced modestly, but significantly. The reaction time (RT) was lower only in the "badly sleeping" group during the second block and higher at the end of the task during the third block after the α-LAC diet, while there were no significant differences after the placebo diet. Thus, there was improvement of the processes of sustained attention by the brain the following morning and, this was accompanied by a better behavioral performance, but only in the group of "bad sleepers".</p>

Chart 1. Characteristics of articles that used human - infants, adults, and the elderly analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and the Capes Journals Portal, between 1998 and 2018. (Continues)

Part A: Articles with human				
Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Aparicio et al., 2007. ¹⁷ Spain	To study the effects on resting-activity cycles in 12 to 20-week-old infants who received milk during periods of light and darkness with different concentrations of tryptophan.	18 healthy infants of both sexes. Age: between 12 weeks (period in which the first signs of biological rhythms begin to be present) and 20 weeks (period in which they are already well established).	<p>Analysis of Tryptophan: Administration of three different milk formulas plus tryptophan: First week (control): Formulation control (commercial infant milk + 1.5g tryptophan / 100g protein per 24h). Second week (reverse control): Control formulation from 6:00 pm to 6:00 am + Enriched formulation (commercial infant milk + 3.4 g tryptophan / 100 g protein) from 6:00 am to 6:00 pm Third week (experimental): Formulation control from 6:00 am to 6:00 pm and Formulation enriched from 6:00 pm to 6:00 am</p> <p>Sleep evaluation: Sleep diary; Actigraphy with weekly records analysis</p> <p>Biochemical analyzes: Analysis of metabolites of catecholamines and serotonins in urine.</p>	<p>In relation to tryptophan: Control week: infants received 1.5% tryptophan (during the day and at night); Experimental week: 2.22% (weighted average) with 1.5% during the day and 3.4% overnight; Reverse control week: average of 2.72%, being 3.4% during the day and 1.5% at night.</p> <p>In relation to sleep: Infants slept the most, had better sleep efficiency, longer immobility, and fewer nighttime movements and wakefulness episodes only when they received the low-dose tryptophan diet during the day and discharge at night.</p> <p>In relation to biochemical data: There was an increase in 5-hydroxy-indole-acetic acid (5-HIAA) and 5-HTP in the urine of infants receiving high amounts of tryptophan overnight.</p>

Chart 1. Characteristics of articles that used human - infants, adults, and the elderly analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and the Capes Journals Portal, between 1998 and 2018. (Continues)

Part A: Articles with human				
Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Cubero et al., 2009. ¹² Spain	To access whether the administration of cereals enriched with sleep-facilitating nutrients could help improve sleep in infants who had sleep disorders at night.	30 infants with sleep disorders (more than 3 nocturnal awakenings). Age: between 8 and 16 months	<p>Analysis of Tryptophan: <u>Sleep-facilitating cereal:</u> standard cereal with 75 mg of tryptophan per 100 g of product, plus 150 mg of tryptophan (final tryptophan concentration of 225 mg per 100 g of product), 5.3 mg of adenosine-5'-P and 6.3 mg of uridine-5'-P, per 100 g of product. Combinations of milk powder and cereals at supper were given at three weeks followed by two weeks apart, totaling 5 weeks. <u>Control week (1st week-red):</u> standard powdered milk + 231.5mg tryptophan, 5.0mg uridine-5'-P and 2.6mg adenosine-5'-P, per 100g product and cereals pattern. <u>Interval week:</u> standard milk administration and standard cereal. <u>Experimental week - cereal sleep (2nd week-green):</u> standard milk powder (= control week) and the cereal formulation facilitating sleep. <u>Interval week:</u> standard milk administration and standard cereal. <u>Experimental week - cereal sleep and milk (3rd week-blue):</u> powdered milk (480mg of tryptophan, 8.8mg of uridine-5'-P and 7.6mg of adenosine-5'-P per 100g of product) and of the sleep-facilitating cereal.</p> <p>Sleep evaluation: Sleep diary and Actigraphy</p>	<p>In relation to sleep: There were significant changes in the blue group in relation to the control group in the parameters (i) minutes of actual sleeping of the infant in the crib at night; (ii) time the infant is sleeping, including the number of awakenings; (iv) minutes of immobilization during the night period; (v) bed time during the night period; and (vii) sleep latency of actimetry.</p>

Chart 1. Characteristics of articles that used human - infants, adults, and the elderly analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and the Capes Journals Portal, between 1998 and 2018. (Continues)

Part A: Articles with human				
Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Bravo et al., 2013. ²¹ Spain	To analyze whether the consumption of cereals enriched with tryptophan, can help reconsolidation of the sleep / wake cycle and counterbalance depression and anxiety.	35 volunteers. Age: 55-75 years	<p>Analysis of Tryptophan: <u>First week (control):</u> standard cereal consumption (22.5 mg tryptophan in 30 g cereals per serving) for breakfast and dinner; <u>Second week (treatment):</u> standard cereal consumption (60mg tryptophan in 30g cereals per serving) for breakfast and dinner; <u>Third week (post-treatment):</u> usual dietary intake, no cereals.</p> <p>Sleep evaluation: Actigraphy for the three weeks to evaluate: time in bed, the difference between onset of sleep and final awakening, real time of sleep, sleep latency, sleep efficiency, number of awakenings, time of immobilization, total activity and index of fragmentation.</p> <p>Biochemical analyzes: Analysis of the metabolites of melatonin (6-sulphatoxymelatonin) and serotonin (5-hydroxyindolacetic acid) in urine and analysis of total antioxidant capacity.</p>	<p>In relation to sleep: The consumption of cereals containing the highest dose of tryptophan significantly increased sleep efficiency, actual sleeping time, immobility time relative to control, and post-treatment. Sleep latency, arousal, total activity and fragmentation index were lower than control values. The values observed in the third week were similar to the values of the control week.</p> <p>In relation to biochemical data: Urinary levels of 6- sulphatoxymelatonin, 5-hydroxyindolacetic acid and total urinary anti-oxidant capacity also increased, respectively, after ingestion of tryptophan enriched cereals.</p>

Chart 1. Characteristics of articles that used human - infants, adults, and the elderly analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and the Capes Journals Portal, between 1998 and 2018. (Continues)

Part A: Articles with human				
Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Wada et al., 2013. ⁶ Japan	To investigate whether a combination of tryptophan-rich breakfast with exposure to sunlight and incandescent light at night could increase melatonin secretion and stimulate earlier sleep times.	63 men belonging to a university football club divided into three groups. Age: 19-22 years.	<p>Analysis of Tryptophan and light exposition: G1 (n = 20) without intervention; G2 (n = 22), breakfast with food rich in protein and vitamin B6 + sun exposure after breakfast; G3 (n = 21), breakfast equal to G2 + sun exposure after breakfast + light exposure incandescent at night. All participants in group G1 and G2 used fluorescent lamps to lighting at night and the G3 group was added incandescent lamp. Implementation score was established for: <u>exposure to sunlight</u> = the sum of days with breakfast with high protein content and exposure to sunlight > 30 minutes; <u>night exposure in incandescent light</u> = average hours per night over the period of the intervention (30 days). Participants who scored the highest rate implementation were considered "high implementation group" and those with low rate "low implementation group".</p> <p>Sleep evaluation: <u>Sleep diary and Questionnaires:</u> Period before and one month after intervention: scale of the diurnal type (Torsvall and Åkerstedt), questions about sleep habits and food habits, and Food Frequency Questionnaire, Questionnaire (self-assessment): Period immediately and one month after intervention: - first point: days in one month of intervention following the recommendations on the content of coffee in the morning; - second point: exposure to sun after breakfast; - third point: use of lamps that emitted light at night.</p> <p>Biochemical analyzes: Analysis of melatonin in saliva samples using an ELISA kit. The samples were collected in 30 participants (10 of each group) the day before the intervention, in 15 days of intervention (midpoint) and on the last day of the intervention.</p>	<p>In relation to sleep: In G3, there was a significant positive correlation between the total number of hours the participants spent at night with incandescent light and the frequency of feeling sleepy during the last week.</p> <p>In relation to biochemical data: The G3 salivary concentration of melatonin was significantly higher than that of G1 and G2 in the combined salivary samplings at the midpoint of the intervention and on the day before the last day of the one-month intervention, whereas no significant differences were found on the day immediately before the beginning of the intervention. In G3, the "high implementation group" tended to show a higher concentration of salivary melatonin at the midpoint of the intervention than the "low implementation group".</p>

Chart 1. Characteristics of articles that used human - infants, adults, and the elderly analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life”, available from PubMed and the Capes Journals Portal, between 1998 and 2018. (Continues)

Part A: Articles with human				
Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Yanamoto et al., 2018. ²⁰ Japan	To analyze the correlation between the adherence to the Japanese Food Guide Spinning Top and the sleep quality.	155 Japanese college students (77 women and 78 men) Age: mean of 20 years old.	<p>Analysis of Tryptophan: A self-administered diet history questionnaire (DHQ) was used to assesses eating behavior, frequency and amount of 110 foods consumed, grain dishes consumed, and dietary supplements consumed per day during the previous 1 month. A Food Guide score, ranging from 0 to 70, was calculated from 7 categories of the Japanese Food Guide Spinning Top and was based on the results from the DHQ. The participants were divided into three groups: T1 group (n = 57) score from 22 to 37 points; T2 group (n = 47) score from 38 to 43 points; and T3 group (n = 51) score from 44 to 62 points.</p> <p>Sleep evaluation: To access the self-rated morningness /eveningness was used a Japanese version of the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) For the assessment of sleep quality, the Japanese version of Pittsburgh Sleep Quality Index (PSQI) was used</p>	<p>In relation to Tryptophan: A higher Food Guide score indicated a higher consumption sources of Trp like meats, fish, eggs, soy products, milk, dairy products and fruits.</p> <p>In relation to sleep: A positive correlation was found between higher habitual dietary quality (assessed by the adherence to the Japanese Food Guide Spinning Top) and better sleep quality measured by MEQ. However, when the PSQI score was used as a continuous variable, the significant correlation weakened.</p>

Source: the authors, based on the study data.

Chart 2. Characteristics of articles that used and animals - rats and ring doves analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life” available from PubMed and the Capes Journals Portal, between 2004 and 2014.

Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
<p>Minet-Ringuet, et al. 2004. ⁸ France</p>	<p>To measure the potential of an α-lactoalbumin enriched diet in order to improve sleep recovery during feedback in adult rats whose sleep duration was previously reduced by 4 days due to total caloric restriction.</p>	<p>18 adults male Wistar rats (<i>Rattus norvegicus</i>)</p>	<p>Tryptophan analysis: Three semisynthetic diets were used after 10 post-operative days: 1-Diet (P14) = P14 (modified AIN-93M diet) + 140g / kg whole milk protein (14% protein). 2-Diet (P30) = P30 + 300g / kg of whole milk protein (30% protein). 3-Diet (P30-α-LAC) = P30 + 300 g / kg whole milk proteins (30% protein) or α-lactalbumin-enriched milk protein extract (> 40%). Periods of supply of the diets: <u>Control period</u> - diet P14 with limited access (55% of daily needs). Start the diet at 6:00 pm, one hour before the lights go out, available throughout the night. The remaining 45% were available between 10h and 12h the following day. <u>Feed restriction period (FR):</u> after the control period, the rats were submitted to 4 days of total feed restriction. <u>Retention period:</u> rat feedback for 6 days with diet P14, P30 and P30-α-LAC. In this period all rats ingested the same amount to evaluate the quality of the diet in the improvement of the sleep. Sleep evaluation or circadian rhythm: <u>Electroencephalogram (EEG):</u> introduction of cortical electrodes for discrimination between sleep states, wakefulness (W), slow sleep waves (SWS) and paradoxical sleep (PS). The duration of the sleep phases was established in \pm 10s.</p>	<p>In relation to sleep <u>Period of food restriction:</u> In this period the duration of W increased twice and there was decrease of SWS and PS for 63 and 49.8% of baseline values, respectively. There was a reduction in the time spent in PS and this was affected mainly by a smaller number of occurrences of PS. Food restriction contributed to the significant increase in the latency period before the first occurrence of an episode of SWS or PS. After 3-4 days of total calorie restriction, there was a reduction in total sleep duration to 50% and a 1,9 increase in sleep latency. <u>Feedback period:</u> The time spent on SWS and W was fully recovered on the first day of feedback in rats with diet P30-α-LAC. In the P14 and P30 rats, the time spent in SWS and W did not return to control values until 4-6 days of feedback, and was better with the P30 diet than with the P14 diet. There was no PS recovery. Sleep recovery progressively occurred in rats fed with 14% or 30% whole milk protein, but was instantaneous in rats fed with 30% α-lactoalbumin.</p>

Chart 2. Characteristics of articles that used and animals - rats and ring doves analyzed for literature review on "Tryptophan-rich diet can influence sleep quality in various phases of the life" available from PubMed and the Capes Journals Portal, between 2004 and 2014. (Continues)

Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
<p>Garau, et al. 2006. ¹⁴ Spain</p>	<p>To evaluate the effects of tryptophan intake on the circadian activity / rest rate and the expression of c-fos in the Suprachiasmatic Nucleus in young and old ring doves.</p>	<p>42 ring doves (<i>Streptopelia risoria</i>) Age: young - 6 months (130g) and the elderly 8-10 years, (170g).</p>	<p>The animals were divided into young (n = 21) and elderly (n = 21) groups, being controlled in relation to temperature, humidity, light / dark cycle of 12/12 h (lights on at 08h daily), fed with poultry and tap water ad libitum.</p> <p>Tryptophan analysis: <u>1st day two hours before the beginning of the dark period:</u> Oral administration of (3% methylcellulose in saline), L-tryptophan (100 and 240mg / kg) or melatonin (2.5 and 5mg / kg) single dose, per day, by esophageal cannula in each animal.</p> <p>After 3 days administration by esophageal cannula: <u>Control animals:</u> vehicle administration (3% methylcellulose in saline solution) in three young and three old animals. <u>Experimental animals:</u> administration of L-tryptophan (240mg / kg) in three young and three old animals or melatonin (5mg / kg) in three young and three old animals.</p> <p>Sleep evaluation or circadian rhythm: <u>Actigraphy</u> to detect the motor activity of animals during 25 days to analyze the effects of L-tryptophan and melatonin at different doses in six young and six elderly animals.</p> <p>Immunohistochemistry analysis: One hour after the lights went out, the animals were operated on. The brains were removed and pinned overnight at 4 ° C, cut into 40 mm thick sagittal slices prior to immunohistochemical processing. Serial sections from each brain were immunostained for c-fos in the previous hypothalamus (including the Suprasquammatic Nucleus-NSQ).</p>	<p>In relation to tryptophan / melatonin: The two concentrations of tryptophan (100 and 240 mg / kg) decreased the nocturnal activity of the young doves in relation to the control; for melatonin concentrations (2.5 and 5 mg / kg), this reduction was similar in both doses. In older animals, both tryptophan and melatonin, only the high dose caused significant reductions in nocturnal activity when compared to control.</p> <p>In relation to sleep or circadian rhythm: Total sleep time was reduced and the number of wakeful bouts was increased in old animals. In older ring doves higher concentrations of tryptophan (240mg / kg) and melatonin (5mg / kg) increased the amplitude of the rest-activity cycle; also increased the efficiency of sleep, resulting from an increase in sleeping hours and a reduction in wakefulness.</p> <p>In relation to histochemistry: Basal immunostaining for the immunoreactivity of c-fos in the previous hypothalamus (including SCN) of elderly ring doves was lower than the young animals. After tryptophan (240mg / kg) and melatonin (5mg / kg) in both young and old ring doves, basal immunostaining for c-fos decreased.</p>

Chart 2. Characteristics of articles that used and animals - rats and ring doves analyzed for literature review on “Tryptophan-rich diet can influence sleep quality in various phases of the life” available from PubMed and the Capes Journals Portal, between 2004 and 2014. (Continues)

Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
Delgado, et al. 2013. ²² Spain	To evaluate the effect of the consumption of a nutraceutical product based on cherry, with high levels of tryptophan, serotonin and melatonin, on the rhythm of activity / rest of nocturnal and diurnal habits, besides the relation with serum melatonin and glucose levels.	Male Wistar rats (<i>Rattus norvegicus</i>) Age: between 6 and 7 months (young, n = 16) and 18 to 20 months (elderly, n = 16) Female and male ring doves (<i>Streptopelia risoria</i>) Age: 4 and 5 years (young, n = 16) and 12 to 14 years (elderly, n = 16).	Analysis of tryptophan: Two groups (control and treated) were divided according to the age group. - Control group - received tap water and fed with ad libitum. - Treatment group - received 27.85g of the diluted nutraceutical mixture in 250ml of water for 10 consecutive days. Sleep evaluation or circadian rhythm: Actigraphy to detect the activity of the animals during the 10 days of treatment and until 3 days after their end. Biochemical analyzes: Analysis of circulating plasma melatonin in the acrophase of the melatonin rhythm in each species. The samples were collected one hour after the lights on, one hour before the lights went out and at 01:30 (time point near the acrophase of the melatonin).	In relation to tryptophan, serotonin and melatonin: In the control group, serum melatonin levels were higher in young animals than in older ones, and were even higher in young animals than in the old group of the treatment group. After the consumption of the nutraceutical product the concentration of serotonin increased in both species and in the groups in relation to age. In relation to sleep or circadian rhythm: The daytime activity in the treatment group of both groups and in both ages was decreased. There was a significant increase in nocturnal activities in young and old rats; opposite effect was found in young and old doves. There was a restoration of the amplitude of the activity rhythm in the old animals in relation to the untreated young animals.

Chart 2. Characteristics of articles that used and animals - rats and ring doves analyzed for literature review on "Tryptophan-rich diet can influence sleep quality in various phases of the life" available from PubMed and the Capes Journals Portal, between 2004 and 2014. (Continues)

Authors/ Year/ Origin	Goals	Sample	Interventions	Synthesis of results
<p>Milagres, et al. 2014. ¹⁵ Brazil</p>	<p>To evaluate the concentration of melatonin in milk collected during milking at night and evaluate its effect with or without tryptophan supplementation on sleep quality in adult rats.</p>	<p>10 Dutch cows used for milking Age: 3 to 7 years (average weight of 580kg) 32 adult male mice (Wistar). Age: 65 days of life (weight between 300 and 350g).</p>	<p>Analysis of tryptophan and melatonin: Rats were divided into four groups (n = 8): <u>Control group:</u> received diet AIN-93M; <u>Groups treatments (groups 1, 2 and 3):</u> diet containing milk from cow milking collected at different times for 28 days. Group 1 (M2h): at 02h; Group 2 (M15h): at 3pm and Group 3 (M2hT): at 02h + tryptophan supplementation (125mg / day-1).</p> <p>Sleep evaluation: <u>Analysis of 6-sulphatoxymelatonin:</u> indirect measurement (alternative to the use of actigraphy) for circadian rhythm control <u>Plasma melatonin analysis:</u> indirect measure correlation with sleep time.</p> <p>Biochemical analyzes: <u>Determination of melatonin concentration in cow's milk:</u> Formulations M15h, M2h and M2hT 6-sulphatoxymelatonin analysis in rat urine (48h) by ELISA.</p>	<p>In relation to tryptophan and melatonin: There was a significant difference between the milking times and the melatonin concentration. The milk concentration obtained at 2h was 39.43pgmL-1, in the one obtained at 15h it was 4.03 pgmL-1.</p> <p>In relation to sleep: Blood melatonin levels and urinary 6-sulfatoxymelatonin values in the M15h group and the control group were found to be similar. However, in the M2h and M2hT groups, blood melatonin concentration and urinary 6-sulfatoxymelatonin levels were higher.</p>

Source: Elaborated by the authors from the study data.

RESULTS

Our search returned a total of 2,830 articles. After applying the inclusion and exclusion criteria, 22 articles remained in the selection. Ten of those were then excluded for being review articles. Thus, 12 articles remained in the study, with eight having been conducted in humans and four in animals.

Charts 1 (in humans) and 2 (in animals) show details on the author, year, origin of the study, objective, sample, strategy employed, and the synthesis of obtained results. Human studies evaluated here were carried out between 1998 and 2018, and those conducted on animals took place between 2004 and 2014.

Of the eight studies performed in humans, two were conducted in children,^{12,17} five in adults^{6,7,18-20} and one in the elderly²¹ (Chart 1). Of the four studies conducted in animals, two evaluated adult animals^{8,15} and the other two were carried out in young and old animals.^{14,22} (Chart 2)

In all studies, the administration of a diet with some source of tryptophan (milk, cereals, fresh or powdered cherries or α -lactalbumin supplementation) during daytime and/or night time in young, adult or elderly individuals (as well as the tryptophan depletion and its reintroduction in elderly individuals) has significantly contributed to the synthesis of chemical mediators such as serotonin and melatonin.

These mediators were evaluated in the plasma and urine and were able to change the chronobiology of the sleep-wake cycle both directly (proven by polysomnography and electroencephalography) and indirectly (proven by actigraphy, questionnaires and sleep diaries), besides interfering with sleep quality of these individuals and/or animals.

DISCUSSION

The studies presented in this review showed that dietary amino acids – particularly tryptophan – increased circulating levels of serotonin and melatonin, which are involved in the sleep-wake cycle regulatory processes in different age groups.

Considering that the circadian rhythm of activity/rest remains non-operative up to approximately the 12th week,¹⁶ or that its operation may be delayed causing sleep disorders,²³ the study by Aparicio et al.¹⁷ showed that when a tryptophan-rich night diet was administered to 12 to 20 weeks-old infants, the consolidation of activity/rest cycle was efficient. Newborns who received higher amounts of tryptophan at night increased the amount of urinary serotonin, which improved the organization of the sleep-wake cycle.

In the study by Cubero et al.,¹² infants who had some type of sleep disorder received milk and cereals enriched with tryptophan at night and, as a result, they stayed longer in bed and had an increased sleep efficiency. There was also an increase in real sleep, sleepiness and nocturnal immobility, with synchronization of the light/dark cycle with that of the family environment.

Another approach to improve sleep quality could be the administration of cow's milk associated with other sources of tryptophan. This option was confirmed in the study by Milagres et al.,¹⁵ who administered cow's milk milked at 2 am and 3 pm to rats. There was an increase in melatonin concentration in the blood of animals that received milk milked at 2 AM supplemented with tryptophan in relation to the one milked at 3 pm, suggesting an improvement in the circadian sleep rhythm of these animals. It is interesting to note that an improvement in the sleep of infants can be obtained by a chronological variation of normal food components, without any pharmacological intervention.

Yet another alternative method is the ingestion of alpha-lactalbumin (α -LAC) protein, which has a high tryptophan content, to increase serotonin concentrations in the brain,²⁴ having been shown to reduce sleep disorders in rats.⁸ Markus et al.¹⁸ added α -LAC to the nocturnal diet of individuals complaining of sleep disorders, and an increase of about 130% in the plasma availability of tryptophan was observed. Moreover, there was an improvement in morning alertness accompanied by better surveillance performance, evidenced by the reduction in reaction times and by the increase in the number of hits in the participants' attention tests. Since nocturnal consumption of α -LAC increased the amount of brain tryptophan and improved the alertness on the following morning, these authors suggested that the night time sleep was healing.

Minet-Ringuet et al.⁸ showed that the administration of α -LAC and whole milk proteins at two different concentrations (140g/kg and 300g/kg) caused a progressive sleep recovery in mice. However, in animals fed α -LAC associated with 30% of protein, sleep recovery was instantaneous, with recovery of slow-wave sleep.

It is known that neutral and high molecular weight amino acids can bind to the same carrier, thus competing with tryptophan.²⁵ So, the passage of tryptophan through the blood brain barrier is influenced by the ratio of tryptophan to those amino acids.^{2,26} However, when α -LAC is administered, this ratio increases 2-3 times and tryptophan is able to reach the brain more swiftly.² Thus, supplementation with α -LAC would be an effective alternative to circumvent some sleep disorders.

The study conducted by Yanamoto et al.²⁰ showed that a higher Food Guide score was related to a better adherence to the Japanese Food Guide Spinning Top, reflecting the intake of a well-balanced diet. The Japanese Food Guide Spinning Top consists of distinct food groups including grains, vegetables, fish and meat, milk, fruits, confectioneries, sugar-sweetened beverages, and alcoholic beverages. Moreover, those individuals with a higher Food Guide score showed better sleep quality.

The authors suggested that the intake of tryptophan might mediate the association between the Food Guide score and sleep quality, as higher Food Guide scores indicate a higher consumption of meats, fish, eggs, soy products, milk and dairy products and also fruits, which are all sources of this amino acid. This study reinforces the role of tryptophan-rich diets in improving sleep quality of young adults, a population particularly vulnerable to the consequences of sleep deprivation, as opposed to older adults.²⁷

Besides measuring the effect of diet on sleep quality, Wada et al.⁶ analyzed a combination of a tryptophan-rich breakfast with exposure to sunlight and incandescent light at night. They found that exposure to light at both periods was able to induce secretion of high amounts of melatonin. The authors brought forward that immediate exposure to the sun after eating a tryptophan-rich breakfast caused an increase in serotonin synthesis.

Rosenthal et al.²⁸ had already considered that the synthesis of serotonin in the pineal gland can occur after exposure to the sun during the day, predominantly in the early hours of the morning. The high synthesis of melatonin at night after nocturnal exposure to low-temperature light is supported by studies that show a high plasma serotonin level at the onset of the dark period caused by the influence of light signals in various brain regions.²⁻⁵ Based on this information, it is believed that the administration of a high-tryptophan diet at breakfast, combined with morning sun exposure and continuity of exposure to low-temperature nighttime light seems to be effective in increasing melatonin secretion, and this could consequently improve sleep quality.

As serotonin is involved in diachronic sleep regulation,^{7,19} two studies evaluated the effect of the rapid depletion of its precursor, *i.e.*, tryptophan, followed by daytime and nighttime re-supplementation over non-REM sleep and REM sleep in adults.

In the study conducted by Arnulf et al.,⁷ the rapid daytime depletion of tryptophan decreased plasma levels both during the day and at night. During the first phase of sleep, increased sleep fragmentation and increased REM sleep latency and density were observed. These authors suggested that serotonergic control of REM sleep latency, unlike sleep events and phasic awakenings, may be dependent on sleep time, and may also be associated with a circadian rhythm that needs to be identified.

Alternatively, REM sleep latency can be controlled by the rate of serotonin synthesis rather than the serotonin level itself. In the study by Voderholzer et al.,¹⁹ depletion of tryptophan with serotonin deficiency caused a decrease in stage 2 of non-REM sleep while increasing wakefulness and reducing the interval between the first and second phases of REM sleep.

In both studies, tryptophan daytime and nighttime re-supplementation may alter the action of serotonin during pregnancy and during sleep through different mechanisms. According to Jouvett's proposition,²⁹ it is important that serotonin be released during the waking period, as it regulates the subsequent synthesis of sleep-inducing factors at night.

Tryptophan deficiency interferes by reducing the length of sleep time and decreasing sleep efficiency in the elderly.^{14,21,22} Elderly individuals studied by Bravo et al.²¹ had problems in initiating and maintaining sleep, so they received tryptophan-enriched cereals at breakfast and at dinner. At higher doses of tryptophan, there was an increase in sleep efficiency, real sleep time, downtime, and a decrease in total nocturnal activity, sleep fragmentation index, and sleep latency.

The effects of tryptophan on the sleep-wake cycle were more significant in sleep regulation, with sleep latency being more attributed to the conversion of this amino acid to serotonin and quality of sleep to the conversion of serotonin to melatonin. On the other hand, the study by Delgado et al.²² used a cherry-based nutraceutical mixture rich in tryptophan, serotonin and melatonin in rats and pigeons - nocturnal and diurnal animals, respectively, and different age groups (young and old). There was an increase in serotonin and melatonin concentrations in both species and in the elderly from both groups, which led to an increase in the nocturnal activity of young and elderly rats, who showed an improvement in motor coordination. The opposite was observed for daytime pigeon activity in both young and old subjects. The amplitude of the activity rhythm was found to be restored in elderly animals in relation to untreated young animals.

Thus, as a prophylactic measure, tryptophan-enriched cereals could be added to the elderly's diet as an attempt to improve changes in the sleep-wake cycle and to control the rhythm of impaired activity/rest in senior animals.

The mechanism involved in the synchronization of the circadian clock in the NSQ for the sleep-wake cycle was evaluated in the study of Garau and coworkers¹⁴ by *c-Fos* expression during the administration of tryptophan in young and old doves. In this study, it was observed that in elderly animals treated with tryptophan and melatonin, the expression of *c-fos* in the early hours of the dark period was reduced, suggesting the activation of NSQ during sleep.

According to Cirelli and Tononi,³⁰ the expression of *c-Fos* protein is high during spontaneous wake or sleep deprivation, being reduced upon a few hours of sleep. In relation to the rhythm of activity/rest, a reduced amplitude was verified in old animals as opposed to younger ones, although this amplitude did increase after the treatments. Moreover, there was an increase in total sleep time and efficiency in elderly animals after treatment. In this study, the NSQ could be indicated as an important target for the effects observed after the treatments with tryptophan and melatonin, reversing, at least in part, some of the disturbances of the circadian cycle of activity/rest related to aging.

All the studies analyzed here revealed that the administration of a diet with some source or supplementation of tryptophan during daytime and/or nighttime in young, adult or elderly individuals and animals contributed to the synthesis of chemical mediators such as serotonin and melatonin, which were able to change the chronobiology of the sleep-wake cycle both directly and indirectly, interfering with sleep quality of these individuals and/or animals.

Although all the diets administered in the aforementioned studies did have some source or supplementation of tryptophan, they were not performed with the same concentrations, nor using similar methodologies, nor in the same period of the day, with some studies being conducted during daytime, others at night, or in both periods. Nevertheless, even if different forms of administration of this amino acid were in fact employed, all of them were able to contribute to the synthesis of chemical mediators such as serotonin and melatonin.

There was, however, no unanimity as to the methodology adopted to evaluate how these mediators changed the chronobiology of the sleep-wake cycle, with some studies approaching it directly and others indirectly.

It is interesting to emphasize that actigraphy was used in six articles,^{12,14,15,17,21,22} with an efficiency improvement in the consolidation of the activity/rest cycle in both humans and animals having been reported by all of them, regardless of the stage of life, that is, from the child to the elderly, and from young to elderly animals. In general, there was greater sleep efficiency, real sleep time, and inactivity time, parallel to a decrease in total night activity, in the sleep fragmentation index and in sleep latency. In all six studies the diet had been enriched or supplemented with tryptophan, although the concentrations and periods of administration differ as expected, due to divergences in age, life stage and type of sample, that is, humans or animals.

In the other two studies^{8,18} tryptophan was administered in a different way, that is, through the intake of alpha-lactalbumin. In both of them, sleep assessment was performed by EEG, but from different points of view. In the first study, which was conducted in animals, EEG was used to verify sleep recovery by the presence of slow-wave sleep. In the second one, conducted in humans, EEC was used to verify the improvement in the morning alertness state accompanied by better surveillance performance associated with other tests.

In addition, in two other studies,^{6,20} tryptophan was indirectly assessed using foods rich in protein, vitamin B6 and foods rich in meat, fish, eggs, soy products, milk, dairy products and fruits. Sleep was assessed using questionnaires on sleep quality and sleep habits, which were not similar. Despite these discrepancies, in both studies, a positive correlation was found between higher quality of diet and better quality of sleep.

Conversely, there was actually tryptophan depletion instead of supplementation in two other studies,^{7,19} with both reporting – through polysomnography – fragmentation of sleep and increased latency and density of REM sleep.

LIMITATIONS

The establishment of the descriptors in the title and/or in the summary of the articles, and the contextualization of the guiding question in the whole of each study, resulted in a reduced sample, in the diversity of the studied population and the range of age groups.

In spite of the methodological specificities employed by the studies to obtain tryptophan (different sources, concentrations, routes and periods of administration, and different methods of analysis) and to

measure sleep or circadian rhythm (different qualitative instruments – questionnaires, scales, sleep, and quantitative variables – actigraphy, EEG, polysomnography), they have all answered the guiding question of this review. That allowed us to appreciate, despite the limitations pointed out, the notable influence that tryptophan – whether supplemented or as a food source – exerts on the circadian sleep-wake rhythm and sleep quality.

CONCLUSION

The quantity and quality of sleep have a great impact on the daily life of all species, and, in humans, fragmented sleep – besides causing various comorbidities – directly affects the capacity for interaction between people. Although the clinical relevance of nutrient intake and sleep has not been established, this integrative review showed the beneficial role of diets enriched with tryptophan or with foods containing high levels of this amino acid, consumed in different periods (diurnal/nocturnal), in structuring the sleep of newborns, improving sleep in adults and in the elderly. Thus, chronobiologically formulated diets with tryptophan used at different day times would increase plasma concentrations of this amino acid and, as a consequence, raise the synthesis of serotonin and melatonin in the brain.

The possible therapeutic proposals advocated in this review are efficient and low-cost alternatives for those who have sleep disorders. These alternatives would also be able to bypass or reduce problems caused by other conditions, such as food restriction, shift work, jet lag and sleep deprivation, which are all socially imposed by modern society.

REFERENCES

1. Matsumoto T, Murase K, Tabara Y, Gozal D, Smith D, Minami T, et al. Impact of sleep characteristics and obesity on diabetes and hypertension across genders and menopausal status: the Nagahama study. *Sleep*. 2018;41(7). <https://doi.org/10.1093/sleep/zsy071>.
2. Peuhkuri K, Sihvola N, Korpela R. Diet promotes sleep duration and quality. *Nutr Res*. 2012; 32(5):309-319. <https://doi.org/10.1016/j.nutres.2012.03.009>. Epub 2012 Apr 25.
3. Kanehisa FM, Tanabe M, Sato Y, Morishima K. KEGG: new perspectives on genomes, pathways, diseases and drugs. *Nucleic Acids Res*. 2017; 45: D353-D361. <https://doi.org/10.1093/nar/gkw1092>. Epub 2016 Nov 28.
4. Mateos SS, Sánchez CL, Paredes SD, Barriga C, Rodríguez AB. Circadian Levels of serotonin in plasma and brain after oral administration of tryptophan in rats. *Basic Clin Pharmacol Toxicol*. 2009; 104(1):52-59. <https://doi.org/10.1111/j.1742-7843.2008.00333.x>.
5. Fernstrom JD. Effects and side effects associated with the non-nutritional use of tryptophan by humans–3. *The J Nutr*. 2012; 142(12):2236S-2244S. <https://doi.org/10.3945/jn.111.157065>. Epub 2012 Oct 17.
6. Wada K, Yata S, Akimitsu O, Krejci M, Noji T, Nakade M, Takeuchi H, Harada T. A tryptophan-rich breakfast and exposure to light with low color temperature at night improve sleep and salivary melatonin level in Japanese students. *J Circadian Rhythms*. 2013; 11:4. <https://doi.org/10.1186/1740-3391-11-4>. eCollection 2013.
7. Arnulf I, Quintin P, Alvarez JC, Vigil L, Touitou Y, Lèbre AS, et al. Mid-morning tryptophan depletion delays REM sleep onset in healthy subjects. *Neuropsychopharmacology*. 2002; 27(5):843-851.
8. Minet-Ringuet J, Le Ruyet PM, Tomé D, Even PC. A tryptophan-rich protein diet efficiently restores sleep after food deprivation in the rat. *Behav. Brain Res*. 2004; 152(2):335–340.
9. Eckel-Mahan K, Sassone-Corsip P. Metabolism and the circadian clock converge. *Physiol Rev*. 2013; 93(1): 107-135. <https://doi.org/10.1152/physrev.00016.2012>.

10. Cubero J, Franco L, Bravo R, Sánchez CL, Rodríguez AB, Barriga C. Chrononutrition: improving infant sleep with tryptophan in food matrices. *J Sleep Dis Ther S*. 2012; 7: 2167-2277. [https://doi.org/ 10.4172/2167-0277.S7-001](https://doi.org/10.4172/2167-0277.S7-001).
11. Aoyama S, Shibata S. Time-of-Day-Dependent Physiological Responses to Meal and Exercise. *Frontiers in Nutrition*. 2020; 7: 18. [https://doi.org/ 10.3389/fnut.2020.00018](https://doi.org/10.3389/fnut.2020.00018).
12. Cubero J, Chanclón B, Sánchez S, Rivero M, Rodríguez AB, Barriga C. Improving the quality of infant sleep through the inclusion at supper of cereals enriched with tryptophan, adenosine-5'-phosphate, and uridine-5'-phosphate. *Nutr Neurosci*. 2009; 12(6):272-280. [https://doi.org/ 10.1179/147683009X423490](https://doi.org/10.1179/147683009X423490)
13. Schneider N, Mutungi G, Cubero J. Diet and nutrients in the modulation of infant sleep: A review of the literature. *Nutr Neurosci*. 2018; 21(3):151-161. [https://doi.org/ 10.1080/1028415X.2016.1258446](https://doi.org/10.1080/1028415X.2016.1258446). Epub 2016 Nov 21.
14. Garau C, Aparicio S, Rial RV, Nicolau MC, Esteban S. Age related changes in the activity-rest circadian rhythms and c-fos expression of ring doves with aging. Effects of tryptophan intake. *Exp Gerontol*. 2006; 41(4):430-438. [https://doi.org/ 10.1016/j.exger.2006.02.003](https://doi.org/10.1016/j.exger.2006.02.003). Epub 2006 Mar 24.
15. Milagres MP, Minim VPR, Minim LA, Simiqueli AA, Moraes LES, Martino HS. Night milking adds value to cow's milk. *J Sci Food Agric*. 2014; 94(8):1688-1692. <https://doi.org/10.1002/jsfa.6480>. Epub 2013 Dec 12.
16. Thomas KA, Burr RL, Spieker S. Light and maternal influence in the entrainment of activity circadian rhythm in infants 4-12 weeks of age. *Sleep Biol Rhythms*. 2016; 14(3):249-255. <https://doi.org/10.1007/s41105-015-0046-2>. Epub 2016 Jan 5.
17. Aparicio S, Garau C, Esteban S, Nicolau MC, Rivero M, Rial RV. Chrononutrition: use of dissociated day/night infant milk formulas to improve the development of the wake-sleep rhythms. Effects of tryptophan. *Nutr Neurosci*. 2007;10 (3-4):137-143. <https://doi.org/10.1080/10284150701455916>.
18. Markus CR, Jonkman LM, Lammers JH, Deutz NE, Messer MH, Rigtering N. Evening intake of α -lactalbumin increases plasma tryptophan availability and improves morning alertness and brain measures of attention. *Am J Clin Nutr*. 2005; 81(5):1026-1033. <https://doi.org/10.1093/ajcn/81.5.1026>.
19. Voderholzer U, Hornyak M, Thiel B, Huwig-Poppe C, Kiemen A, König A, et al. Impact of experimentally induced serotonin deficiency by tryptophan depletion on sleep EEG in healthy subjects. *Neuropsychopharmacology*. 1998; 18(2):112-124. [https://doi.org/ 10.1016/S0893-133X\(97\)00094-8](https://doi.org/10.1016/S0893-133X(97)00094-8).
20. Yamamoto K, Ota M, Minematsu A, Motokawa K, Yokoyama Y, Yano T, Watanabe Y, Yoshizaki T. Association between Adherence to the Japanese Food Guide Spinning Top and Sleep Quality in College Students. *Nutrients*. 2018; 10(1996). [https://doi.org/ 10.3390/nu10121996](https://doi.org/10.3390/nu10121996).
21. Bravo R, Matito S, Cubero J, Paredes SD, Franco L, Rivero M, et al. Tryptophan-enriched cereal intake improves nocturnal sleep, melatonin, serotonin, and total antioxidant capacity levels and mood in elderly humans. *Age (Dordr)*. 2013; 35(4):1277-1285. [https://doi.org/ 10.1007/s11357-012-9419-5](https://doi.org/10.1007/s11357-012-9419-5). Epub 2012 May 24.
22. Delgado J, Terrón MP, Garrido M, Pariente JA, Barriga C, Rodríguez AB, et al. Diets enriched with a Jerte Valley cherry-based nutraceutical product reinforce nocturnal behaviour in young and old animals of nocturnal (*Rattus norvegicus*) and diurnal (*Streptopelia risoria*) chronotypes. *J Anim Physiol Anim Nutr (Berl)*. 2013; 97(1):137-145. <https://doi.org/10.1111/j.1439-0396.2011.01251.x>. Epub 2011 Nov 10.
23. Pin Arboledas G. The sleep in children with neurodevelopmental disorders. *Medicina*. 2019;79(1):44-50
24. Citraro R, Scicchitano F, De Fazio S, Raggio R, Mainardi P, Perucca E, et al. Preclinical activity profile of α -lactoalbumin, a whey protein rich in tryptophan, in rodent models of seizures and epilepsy. *Epilepsy Res*. 2011;95(1-2):60-69. <https://doi.org/10.1016/j.eplepsyres.2011.02.013>. Epub 2011 Apr 1
25. Fernstrom JD. Large neutral amino acids: dietary effects on brain neurochemistry and function. *Amino Acids*. 2013;45(3):419-430. <https://doi.org/10.1007/s00726-012-1330-y>. Epub 2012 Jun 8.
26. Fernstrom JD, Langham KA, Marcelino LM, Irvine ZL, Fernstrom MH, Kaye WH. The ingestion of different dietary proteins by humans induces large changes in the plasma tryptophan ratio, a predictor of brain tryptophan uptake and serotonin synthesis. *Clin Nutr*. 2013;32(6):1073-1076. [https://doi.org/ 10.1016/j.clnu.2012.11.027](https://doi.org/10.1016/j.clnu.2012.11.027). Epub 2013 Jan 23.
27. Schwarz J, Axelsson J, Gerhardsson A, Tamm S, Fischer H, Kecklund G, Åkerstedt T. Mood impairment is stronger in young than in older adults after sleep deprivation. *J. Sleep Res*. 2018; e12801. [https://doi.org/ 10.1111/jsr.12801](https://doi.org/10.1111/jsr.12801).
28. Rosenthal N, Schwartz P, Turner E, Naim S, Matthews J, Hardin T, et al. The psychobiology of SAD and the mechanism of action of light therapy. *Biol Psychiatry*. 1997; 42(1): 42-57.

29. Jouvet M. Indolamines and sleep-inducing factors. *Exp. Brain Res.* 1984 suppl. 8: 81–94.
30. Cirelli C, Tononi G. On the functional significance of c-fos induction during the sleep-waking cycle. *Sleep.* 2000; 23(4): 9-25.

Contributors

Araújo MTM, Guandalini VR and Polese JF contributed to the design of the study; Araújo MTM, Franchini M and Marins L contributed to obtain the data; Araújo MTM, Franchini M, Marins L and Coitinho JB contributed to the analysis and interpretation of the data and contributed to the writing of the manuscript; Araújo MTM, Guandalini VR, Polese JF and Coitinho JB contributed to the critical review of the manuscript regarding the important intellectual content; Araújo MTM contributed with the supervision of the study.

Conflict of Interest: The authors declare no conflict of interest.

Received: July 31, 2019

Accepted: May 29, 2020