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Biologically Active Substances and Sleep

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The influences of dietary characteristics on sleep quality in humans currently constitute an acute problem, as harmonious interactions with the outside world in urbanized societies impose the need for a sufficient level of wakefulness, which is provided by full-length sleep. An important factor is sleep quality: fragmented sleep, regardless of duration, will leave a person lacking energy. Sleep quality depends not only on sleep hygiene, but also on the characteristics of the diet, which can affect the proportions of particular phases and stages of sleep. The aim of this review is to discuss the most important studies on the effects of dietary supplements on sleep quality and duration.

Keywords: sleep, insomnia, obstructive sleep apnea syndrome, diet, carbohydrates, amino acids.

The problem of sleep disorders is currently among the most significant in modern medicine and is actively studied in the scientific community. It was previously believed that lack of sleep had only immediate consequences, in the form of excessive daytime sleepiness, impairments to attention and other cognitive functions, and decreased physical activity during the day. However, this view began to change with time. Studies reported by Taheri et al. in 2004 [1] revealed an association between increased ghrelin levels and decreased plasma leptin levels on the one hand and reduced sleep duration on the other, and these changes lead to an increase in appetite, which in turn is an independent risk factor for obesity [1]. Insufficient sleep has also been shown to be a risk factor for type 2 diabetes mellitus (DM2) and reduced glucose tolerance. As demonstrated by Gottlieb et al. [2], shorter nocturnal sleep is associated with a greater risk of developing DM2: nocturnal sleep duration of less than 6 hours increases the risk by factor of 1.7, while sleep lasting less than 5 hours produces a 2.5-fold increase compared with people who sleep more than seven hours per day [2]. Sleep is also essential for maintaining mental health in children and adolescents, as well as adults.

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Among all sleep disorders, the most common at this time are insomnia, with prevalence in the adult population ranging from 10% to 30% in different reports [3], along with obstructive sleep apnea syndrome (OSAS), which occurs in approximately 17% of the adult population [4]. Both conditions are characterized by insufficient sleep, which results in an increased risk of dysmetabolic disorders in the form of DM2, glucose tolerance, and obesity.

There is an undoubted relationship between sleep disorders and eating disorders. However, the following questions remain open: can eating behavior and dietary patterns affect sleep quality in any way? Can changing the diet and adding particular substrates to it affect sleep duration?

The first attempts to study the effects of adding amino acids (5-hydroxytryptophan, 5-HTP) to food date back to 1969 [5]. This was linked with the hypothesis put forward at that time by Jouvet that serotonin is a "sleep factor." This hypothesis was based on a series of studies conducted in his laboratory showing that administration of the serotonin synthesis blocker para-chlorophenylalanine to cats led to prolonged total insomnia in the animals, which was stopped by giving the serotonin precursor 5-HTP. This hypothesis was later recognized as erroneous, and serotonin is presently regarded mainly as a "waking factor" [6].

A major review was published in 1987 describing the effects of tryptophan and carbohydrates on the duration and architecture of sleep [7]. The last 20 years have seen intense

studies of the influences of dietary features on sleep quality and duration, including the influences of food carbohydrate, fat, and protein contents, as well as the supplementary consumption of sleep-inducing amino acids [8]. The aim of this review is to discuss data from the most important studies on the influences of dietary characteristics on sleep quality and duration.

Carbohydrates. The main focus of research attention has been on the effects of carbohydrate content – the main source of energy in food – on sleep quality. Studies reported by Phillips et al. [9] in 1975 compared the effects of high- and low-carbohydrate diets on sleep. The study included eight volunteers, who were presumptively healthy men without bad habits or eating disorders, and a specific nutrition program was developed for each subject, which included changing the diet from a low-carbohydrate diet (100 g/day) to a high-carbohydrate diet (600 g/day) with subsequent assessment of sleep polysomnography. This showed that the high-carbohydrate diet led to a significant decrease in the proportion of stage III slow-wave sleep (SWS); this was accompanied by a decrease in rapid eye movement (REM) sleep as compared with the low-carbohydrate diet [9].

Another study, reported by Afaghi et al. [10], assessed not only the relationship between the ratios of SWS and REM sleep, but also sleep latency. A group of 12 men aged 18–35 years took part in the study, which assessed the effects of eating a high glycemic index (GI) food compared with a low GI food, with consumption of an equal quantity of calories (GI is a dimensionless coefficient reflecting the rate at which carbohydrates present in food increase the blood glucose level as compared with glucose itself, which has a GI of 100). Thus, it has been demonstrated that sleep latency was found to be significantly reduced (9.0 ± 6.2 min) after consuming a high GI meal as compared with a low-GI meal (17.5 ± 6.2 min) [10]. Furthermore, Tanaka et al. [11] ran a comparative assessment of sleep quality in relation to eating habits in a large cohort of volunteers. This study assessed the eating habits of 4,435 non-shift workers. The following relationship was found: habitual consumption of food with a low carbohydrate content (less than 50% of the energy of the daily diet) and high protein content (more than 16% of the energy of the daily diet) was associated with more frequent night awakenings, while consumption of food with a low protein content (less than 16% of daily energy intake) was associated with difficulty falling asleep, as well as with poorer sleep quality [11]. Contrarily, Gangwisch et al. [12] reported studies assessing the effects of the quantitative carbohydrate content in the daily diet on the risk of developing symptoms of insomnia in postmenopausal women. High carbohydrate intake was found to be associated with a greater risk of developing symptoms of insomnia in this cohort [12].

The effect of high carbohydrate content on sleep in humans can be summarized as follows: use of a high-carbohydrate diet shortens REM sleep, lengthens stages I and II of SWS, and shortens sleep latency. However, what is the mechanism of this effect of dietary carbohydrate content on sleep in humans? One hypothesis holds that high-GI food causes consistent increases in the blood insulin level, which in turn improves the consumption of large neutral amino acids (phenylalanine, leucine, isoleucine, tyrosine, valine, and methionine) by muscle tissue [13]. The result of this action of insulin is that the relative tryptophan content in the circulating blood increases, leading to an increase in its consumption in the brain [10, 13]. Tryptophan is a serotonin precursor, and some data suggest that increases in serotonin promote the onset of falling asleep [10].

Amino acids. γ-Aminobutyric acid (GABA) is a four-carbon amino acid, which is not involved in making proteins in the body but is present in food. This amino acid was isolated from the mammalian brain in 1950 by a group of researchers led by Roberts and Frankel [14]. GABA was also found to be a brain-specific marker. GABA is the only neurotransmitter that is found almost exclusively in this part of the CNS (a small amount of GABA is also found in the cervical segments of the spinal cord), where its concentration exceeds that of all other low-molecular-weight mediators combined. GABA is the main inhibitory neurotransmitter in the brain [14, 15]. It was long believed that GABA consumed with food does not cross the blood–brain barrier (BBB) [16], though studies in the late 1990s discovered specific GABA transporters on the surfaces of BBB cells [17]. However, there are as yet no reliable data confirming that there is a correlation between GABA concentrations in the blood and CNS tissues [18].

The functions of GABA include regulation of the body's response to stress and anxiety via GABAergic interneurons located in the amygdala [19]; this type of neuron in the corticomedullary pathways is believed to regulate the ratio of SWS and REM sleep [20]; these neurons also regulate the daily sleep/waking rhythm via influences on the suprachiasmatic nuclei (SCN) [21]. Considering these functions of GABAergic neurons, there is interest in studying the effects of GABA, as an independent biological supplement, on the objective characteristics of sleep and sleep quality in terms of subjective assessments.

Thus, studies reported by Yamatsu et al. [18] assessed the effect of supplementing the diet of healthy volunteers with 100 mg GABA as capsules taken in the second half of the day, as compared with a second group receiving placebo. These studies revealed the following patterns: GABA intake significantly reduced sleep latency by 5 min as compared with the control group. Mean sleep latency was 10 min in both groups prior to the supplementation with GABA-containing capsules. Furthermore, the latency of stage II SWS was lower in volunteers who took GABA (by an average of 4.8 min). Subjective sleep indicators such as feelings after waking and Pittsburgh Sleep Quality Index (PSQI) questionnaire scores were significantly better in volunteers who took GABA than in the placebo group [18].

Another study, reported by Byun et al. [22], evaluated the effects of daily dietary supplementation with GABA (300 mg) on symptoms of insomnia. This study included 40 volunteers, 30 receiving GABA and 10 receiving placebo. Each subject underwent sleep quality assessment before and after use of GABA, along with polysomnography to exclude other causes of daytime sleepiness and sleep disturbance. GABA supplementation for four weeks decreased the ISI score (from 14.6 ± 6 before treatment compared with 11.5 ± 4.3 after treatment for four weeks) and the PSQI score (from 11.0 ± 2.2 before treatment to 9.8 ± 2.5 after treatment). There was also a reduction in sleep latency on the polysomnogram, from 13.4 ± 15.7 min before treatment started to 5.7 ± 6.2 min after four-week courses of GABA [22].

Another product with a potential effect on sleep and of interest to researchers is glycine. Glycine is a non-essential amino acid (it is ingested with food or synthesized de novo in the human body) with the simplest molecular structure. Glycine is one of the most common inhibitory neurotransmitters in the CNS, its the mechanism of action being mediated by glycine receptors (GlyR) [23]; it is also a coagonist on stimulation of *N*-methyl-*D*-aspartate (NMDA) receptors [24]. One of the main effects of glycine is to decrease skin surface temperature, which is followed by reflex vasodilation of skin vessels and subcutaneous fatty tissue, which then leads to hypoperfusion of the brain, resulting in drowsiness [25].

The effects of taking glycine on volunteers with complaints of poor sleep quality were studied by Inagawa et al. [26], who evaluated the effects of glycine (3 g) before sleeping as compared with a group of volunteers taking a placebo. Glycine was found to produce significant reductions in anxiety levels the morning after intake and to improve subjective sleep scores in volunteers who took glycine (3 g) at night [26].

The effects of 5-HTP on sleep are also of particular interest [6]. 5-HTP is a product of the hydroxylation reaction of the amino acid tryptophan. 5-HTP is then decarboxylated to 5-hydroxytyramine, better known as serotonin. Serotonin has a wide spectrum of actions in the CNS: it is involved in memory processes, stress responses, and mood regulation; it influences sleep and the process of maintaining wakefulness [27]. 5-Hydroxytyramine is subsequently metabolized to melatonin (*N*-acetyl-5-methoxytryptamine), which is a hormone secreted by the pineal gland and is involved in the regulation of the sleep–waking cycle [28].

Early studies of the effects of 5-HTP date back to the 1950s, when animal experiments showed that 5-HTP inhibited gastric acid secretion [29], stimulated gastrointestinal motility [30], and also, as noted, increased the 5-HTP concentration in most peripheral organs and tissues after administration [31]. Rabbit experiments reported by Banerjee et al. [32] in the 1970s demonstrated a hypothermic effect of 5-HTP given at a dose of 1.5–3 mg [32].

As 5-HTP is a precursor of serotonin, one of the main objects of research in the early stages of studying its effect on the human body addressed its effects on depressive episodes. Thus, Coppen et al. [33] showed that 5-HTP had an antidepressant effect when given at high doses. Another study, reported by Kahn et al. [34], demonstrated that 5-HTP had anxiolytic effects in a situational anxiety test.

Evaluation of the effects of 5-HTP on sleep found an effect on the proportion of REM sleep: increases in the 5-HTP dose produced proportionate increases in the duration of this sleep phase [35]. 5-HTP has been shown to be effective in relation to nightmares in children: Bruni et al. [36] showed that daily administration of 5-HTP both increased daytime wakefulness and decreased the frequency of nocturnal nightmares in children.

A double-blind, placebo-controlled study found that blood 5-HTP levels were directly proportional to sleep latency in healthy subjects [37]. A Japanese study of the effects of 5-HTP on daytime wakefulness and nocturnal sleep in children aged 0–15 years found that daily intake of 5-HTP in the morning maintained the morning chronotype in children and also produced an improvement in the quality of nocturnal sleep [38].

Conclusions. Consumption of a number of foodstuffs can, due to their greater or lesser contents of certain amino acids or carbohydrates, affect sleep quality and duration. Studies have shown that increases in carbohydrate intake can lead to sleep disturbance and may be a risk factor for the development of insomnia. Studies addressing the relationship between sleep indicators and amino acid intake have shown that amino acids such as GABA, glycine, and 5-HTP can influence objective and subjective measures of sleep.

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REFERENCES

1. S. Taheri, L. Lin, D. Austin, et al., "Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index," *PLoS Med.*, **1**, No. 3, e62 (2004), https://doi.org/10.1371/journal.pmed.0010062.
2. D. Gottlieb, N. Punjabi, A. Newman, et al., "Association of sleep time with diabetes mellitus and impaired glucose tolerance," *Arch. Int. Med.*, **165**, No. 8, 863–867 (2005), https://doi.org/10.1001/archinte.165.8.863.
3. S. Bhaskar, D. Hemavathy, and S. Prasad, "Prevalence of chronic insomnia in adult patients and its correlation with medical comorbidities," *J. Family Med. Prim. Care*, **5**, No. 4, 780–784 (2016), https://doi.org/10.4103/2249-4863.201153.
4. C. Senaratna, J. Perret, C. Lodge, et al., "Prevalence of obstructive sleep apnea in the general population: A systematic review," *Sleep Med. Rev.*, **34**, 70–81 (2017), Epub July 18, 2016, https://doi.org/10.1016/j.smrv.2016.07.002.
5. O. Petre-Quadens and C. Lee, "5-Hydroxytryptophan and sleep in Down's syndrome," *J. Neurol. Sci.*, **26**, No. 3, 443–453 (1975), https://doi.org/10.1016/0022-510x(75)90213-0.
6. V. M. Kovalzon, "Serotonin, sleep and depression: a hypothesis," in: *Serotonin and the CNS – New Developments in Pharmacology and Therapeutics*, B. Olivier (ed.), IntechOpen, London (2021), https://doi.org/10.5772/intechopen.96525.

7. B. Spring, J. Chiodo, and D. Bowen, "Carbohydrates, tryptophan, and behavior: A methodological review," *Psychol. Bull.*, **102**, No. 2, 234–256 (1987), https://doi.org/10.1037/0033-2909.102.2.234.
8. M. Zhao, H. Tuo, S. Wang, et al., "The effects of dietary nutrition on sleep and sleep disorders," *Mediat. Inflamm.*, **2020**, Article ID 3142874 (2020), https://doi.org/10.1155/2020/3142874.
9. F. Phillips, A. Crisp, B. Mcguinness, et al., "Isocaloric diet changes and electroencephalographic sleep," *Lancet*, **306**, No. 7938, 723–725 (1975), https://doi.org/10.1016/s0140-6736(75)90718-7.
10. A. Afaghi, H. O'Connor, and C. Chow, "High-glycemic-index carbohydrate meals shorten sleep onset," *Am. J. Clin. Nutr.*, **85**, No. 2, 426–430 (2007), https://doi.org/10.1093/ajcn/85.2.426.
11. E. Tanaka, H. Yatsuya, M. Uemura, et al., "Associations of protein, fat, and carbohydrate intakes with insomnia symptoms among middle-aged Japanese workers," *J. Epidemiol.*, **23**, No. 2, 132–138 (2013), https://doi.org/10.2188/jea.je20120101.
12. J. Gangwisch, L. Hale, M. St-Onge, et al., "High glycemic index and glycemic load diets as risk factors for insomnia: analyses from the Women's Health Initiative," *Am. J. Clin. Nutr.*, **111**, No. 2, 429–439 (2020), https://doi.org/10.1093/ajcn/nqz275.
13. R. Wurtman, J. Wurtman, M. Regan, et al., "Effects of normal meals rich in carbohydrates or proteins on plasma tryptophan and tyrosine ratios," *Am. J. Clin. Nutr.*, **77**, No. 1, 128–132 (2003), https://doi.org/10.1093/ajcn/77.1.128.
14. E. Roberts and S. Frankel, "Gamma-aminobutyric acid in brain: its formation from glutamic acid," *J. Biol. Chem.*, **187**, 55–63 (1950).
15. O. Petroff, "GABA and glutamate in the human brain," *Neuroscientist*, **8**, 562–573 (2002), https://doi.org/10.1177/1073858402238515.
16. K. Kuriyama and P. Sze, "Blood–brain barrier to H3-γ-aminobutyric acid in normal and amino oxyacetic acid-treated animals," *Neuropharmacology*, **10**, 103–108 (1971), https://doi.org/10.1016/0028-3908(71)90013-X.
17. M. Bassett, K. Mullen, B. Scholz, et al., "Increased brain uptake of γ-aminobutyric acid in a rabbit model of hepatic encephalopathy," *Gastroenterology*, **98**, 747–757 (1990), https://doi.org/10.1016/0016-5085(90)90298-F.
18. A. Yamatsu, Y. Yamashita, T. Pandharipande, et al., "Effect of oral gamma-aminobutyric acid (GABA) administration on sleep and its absorption in humans," *Food Sci. Biotechnol.*, **25**, 547–551 (2016), https://doi.org/10.1007/s10068-016-0076-9.
19. P. Nuss, "Anxiety disorders and GABA neurotransmission: a disturbance of modulation," *Neuropsychiatr. Dis. Treat.*, **11**, 165–175 (2015), https://doi.org/10.2147/NDT.S58841.
20. P.-H. Luppi, C. Peyron, and P. Fort, "Not a single but multiple populations of GABAergic neurons control sleep," *Sleep Med. Rev.*, **32**, 85–94 (2017), https://doi.org/10.1016/j.smrv.2016.03.002.
21. D. DeWoskin, J. Myung, M. Belle, et al., "Distinct roles for GABA across multiple timescales in mammalian circadian timekeeping," *Proc. Natl. Acad. Sci. USA*, **112**, 3911–3919 (2015), https://doi.org/10.1073/pnas.1420753112.
22. J. Byun, Y. Shin, S. Chung, et al., "Safety and efficacy of gamma-aminobutyric acid from fermented rice germ in patients with insomnia symptoms: A randomized, double-blind trial," *J. Clin. Neurol.*, **14**, No. 3, 291–295 (2018), https://doi.org/10.3988/jcn.2018.14.3.291.
23. S. Rajendra, J. Lynch, and P. Schofield, "The glycine receptor," *Pharmacol. Ther.*, **73**, 121–146 (1997), https://doi.org/10.1016/s0163-7258(96)00163-5.
24. P. Leeson and L. Iversen, "The glycine site on the NMDA receptor: structure-activity relationships and therapeutic potential," *J. Med. Chem.*, **37**, 4053–4067 (1994), https://doi.org/10.1021/jm00050a001.
25. N. Kawai, M. Bannai, and M. Takahashi, "Glycine decreases core body temperature and increases cutaneous blood flow via NMDA receptors in rats," Program No. 276.7/DD68, 2009 Neuroscience Meeting Planner, Society for Neuroscience, Chicago, IL (2009), Online.
26. K. Inagawa, T. Hiraoka, T. Kohda, et al., "Subjective effects of glycine ingestion before bedtime on sleep quality," *Sleep Biol. Rhythms*, **4**, 75–77 (2006).
27. D. Štrac, N. Pivac, and D. Mück-Šeler, "The serotonergic system and cognitive function," *Transl. Neurosci.*, **7**, No. 1, 35–49 (2016), https://doi.org/10.1515/tnsci-2016-0007.
28. T. Ye, X. Yin, L. Yu, et al., "Metabolic analysis of the melatonin biosynthesis pathway using chemical labeling coupled with liquid chromatography-mass spectrometry," *J. Pin. Res.*, **66**, 11 (2019), https://doi.org/10.1111/jpi.12531.
29. A. Smith, W. Black, and E. Fisher, "Inhibitory effect of 5-hydroxytryptophan on acid gastric secretion," *Nature*, **180**, 1127 (1957), https://doi.org/10.1038/1801127a0.
30. E. Bulbring and R. Lin, "The effect of intraluminal application of 5-hydroxytryptamine and 5-hydroxytryptophan on peristalsis; the local production of 5-ht and its release in relation to intraluminal pressure and propulsive activity," *J. Physiol.*, **140**, 381–407 (1958).
31. S. Udenfriend, H. Weissbach, and D. Bogdanski, "Increase in tissue serotonin following administration of its precursor 5-hydroxytryptophan," *J. Biol. Chem.*, **224**, 803–810 (1957).
32. U. Banerjee, T. Burks, W. Feldberg, et al., "Temperature responses and other effects of 5-hydroxytryptophan and 5-hydroxytryptamine when acting from the liquor space in unanaesthetized rabbits," *Br. J. Pharmacol.*, **38**, 688–701 (1970), https://doi.org/10.1111/j.1476-5381.1970.tb09877.x.
33. A. Coppen, D. Shaw, and A. Malleson, "Changes in 5-hydroxytryptophan metabolism in depression," *Br. J. Psychiatry*, **111**, 105–107 (1965), https://doi.org/10.1192/bjp.111.470.105.
34. R. Kahn, H. Westenberg, W. Verhoeven, et al., "Effect of a serotonin precursor and uptake inhibitor in anxiety disorders-a double-blind comparison of 5-hydroxytryptophan, clomipramine and placebo," *Int. Clin. Psychopharmacol.*, **2**, 33–45 (1987), https://doi.org/10.1097/00004850-198701000-00003.
35. R. Wyatt, V. Zarcone, K. Engelman, et al., "Effects of 5-hydroxytryptophan on the sleep of normal human subjects," *Electroencephalogr. Clin. Neurophysiol.*, **30**, 505–509 (1971), https://doi.org/10.1016/0013-4694(71)90147-7.
36. O. Bruni, R. Ferri, S. Miano, and E. Verrillo, "L-5-hydroxytryptophan treatment of sleep terrors in children," *Eur. J. Pediatr.*, **163**, 402–407 (2004), https://doi.org/10.1007/s00431-004-1444-7.
37. C. George, T. Millar, P. Hanly, et al., "The effect of L-tryptophan on daytime sleep latency in normals: correlation with blood levels," *Sleep*, **12**, No. 4, 345–353 (1989).
38. T. Harada, M. Hirotani, M. Maeda, et al., "Correlation between breakfast tryptophan content and morning-evening in Japanese infants and students aged 0–15 yrs," *J. Physiol. Anthropol.*, **26**, No. 2, 201–207 (2007).