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Review Article

Potential Role of Butyrate Fermented in Aloe Vera Gel for Enough Sleeping as an Adjuvant

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Abstract

Case Report-1: A 70-years-old male who has a daily busy work, took several times triazolam, because of bad sleeping, but he felt dizzy on October, 2018. Then he started to drink Aloe vera juice (AVJ) 200 ml/day with triazolam and then he took AVJ without triazolam on May, 2019. He has a good sleeping and well-being on June, 2023. Case report-2: A 65-years-old-female who prescribed eszopiclone, because of mental disorders, mental illness and insomnia on November 2019, showed some menopausal disorders. Then, she subscribed eszopiclone and Kampo: Kamishyoyo-san with AVJ 300 ml/d. Since then, she had a good 7-hours-sleeping without eszopiclone on June, 2016. Now, she had a good 6-hours-sleeping without Kampo: Kamishyoyo-san, only taking AVJ 500 ml/d. on April, 2018. Case report-3: A 60-years-old female who has a busy work and was insomnia and hypothermia, and 3 - 4 hours-sleeping. Then, she was subscribed etizolam. And she started to drink Kampo: Kamishyosy-san with AVJ 500 ml/d. and etizolam every other day on June, 2016. Then, her body temperature recovered ~36°C and she had a good sleeping time (6 - 7 hours) without etizolam on April, 2018. Case report-4: A 40-years-old female takes caring her child, who had 3 - 4 hours-sleeping time, because of excessively sensitive. She started to drink AVJ 200ml/d. when put a child to sleep, and had a good sleeping time (7 hrs.) on April, 2020. Now she has a good health conditioning and well mental stability on April, 2023. Case report-5: A 80-years-old male who had diagnosed sleep-inducing drug and obstructive sleep apnea-induced hypertension in his ill-history during his hard works, started to drink AVJ 200 ml/d. as an adjuvant with the drugs under walking-exercise on June, 2023. He has a good sleeping with the hypertensive drug without sleep-inducing drug and AVJ ingestion as an adjuvant, and is a well-being health in Augst, 2023.

Keywords: *Butyrate Fermented; Aloe Vera Gel; Sleeping; Adjuvant*

Introduction

Sleeping inducing drug (17.6%, N = 2733) is located second level in the drug dependence patients based upon the field study of drug related psychiatric disorder in psychiatric health facilities in Japan on 2020, while the psychostimulant was the first level, 53.5% [1]. Medical herbalist N. Parkar explains how gut health can affect your sleep. Parkar., *et al*. [2] examined how gut bacteria processes their own daily rhythmicity in terms of composition, their localization to intestinal niches, and functions. The author reviewed evidence that

gut bacteria modulate host rhythms via microbial metabolites such as butyrate, polyphenolic derivatives, vitamins, and amines. Lifestyle stressors such as altered sleep and eating patterns that may disturb the host circadian system also influence the gut microbiome. Disturbances in microbiome rhythms may at least partially contribute to an increased risk of obesity and metabolic syndrome, associated with insufficient sleep and circadian misalignment. Good sleep and a healthy diet appear to be essential for maintaining gut microbial balance. Manipulating daily rhythms of gut microbial abundance and activity may therefore hold promise for a chrono-nutrition-based approach to consolidate host circadian rhythms and metabolic homeostasis. Ogawa., *et al*. [3] examined the effects of the gut microbiota on sleep/wake regulation. C57BL/6 male mice were treated with broad-spectrum antibiotics for 4 weeks to deplete their gut microbiota. Metabolome profiling of cecal contents in antibiotic-induced microbiota-depleted (AIMD) and control mice showed significant variations in the metabolism of amino acids and vitamins related to neurotransmission, including depletion of serotonin and vitamin B6, in the AIMD mice. Sleep analysis based on electroencephalogram and electromyogram recordings revealed that AIMD mice spent significantly less time in non-rapid eye movement sleep (NREMS) during the light phase while spending more time in NREMS and rapid eye movement sleep (REMS) during the dark phase. The gut microbiota is suggested to affect the sleep/wake architecture by altering the intestinal balance of neurotransmitter. Sen., *et al*. [4] explore how the microbiota-gut-brain axis affects sleep directly and indirectly. The author summarized the possible molecular mechanisms underlying sleep-microbiome interactions and discuss how various factors interact with the gut microbiota to in influence sleep. Furthermore, the authors present the current evidence of alterations of the microbiota-gut-brain axis in various sleep disorders and pathologies where comorbid sleep disturbances are common. Since manipulating the gut microbiota could potentially improve sleep, the author outline ways in which this can be achieved. Szentimal., *et al*. [5] reviewed that how bacterial metabolites and components of the bacterial cell wall are likely to provide important signals. Butyrate is a short-chain fatty acid produced by the intestinal bacteria by the fermentation of nondigestive polysaccharides. The author tested the hypothesis that butyrate may serve as a bacterial-derived sleep-promoting signal. Oral gavage administration of tributyrin, a butyrate pro-drug, elicited an almost 50% increase in non-rapid-eye movement sleep (NREMS) in mice for 4 hours after the treatment. Similarly, injection of butyrate led to prompt and robust increases in NREMS in rats. In the first 6 hours after the butyrate injection, NREMS increased by 70%. Both the oral and intraportal administration of butyrate led to a significant drop in body temperature. In intraportal administration of butyrate led to a significant drop in body temperature. The result suggested that the sleep-inducing effects of butyrate are mediated by a sensory mechanism located in the liver and/or in the portal vein wall. Hepatoportal butyrate-sensitive mechanisms may play a role in sleep modulation by the intestinal microbiota.

Wang., *et al*. [6] in indicate described the bidirectional relationships between sleep and gut microbiota and summarized the abnormal characteristics of gut bacterial in in distinct conditions including sleep disturbances, sleep disorders and sleep disorders comorbid with neuropsychiatric disorders. The authors examined the potential routes of microbiota-gut-brain axis in sleep and gut microbiome interactions, including metabolic, immune, and neural pathways, and proposed microbiota-targeted interventions for improving sleep. Manipulating gut microbiota may be a promising avenue for the development of novel interventions for sleep disorders.

Present review article indicated that how Aloe vera juice (AVJ) ingestion as an adjuvant ameliorated insufficient sleep, insomnia drugs multi-treatment, and mental disorders in case reports 1-5, and how higher butyrate leveled the increase duration of deep on-rapid eye movement sleep, and the enough sleeping.

Insufficient sleep is a key factor in the occurrence of intestinal diseases

Gao., *et al*. [7] performed how sleep deficiency mediates the intestinal microbiota, metabolites butyrate disturbance induces intestinal mucosal damages, and butyrate ameliorates it. Twenty-two healthy volunteers were interviewed, and the influence of insufficient sleep on the gut microbiota and metabolite composition was explored. Moreover, a-72-h sleep deprivation (SD) mouse model with or without butyrate supplementation was used to reveal the effect of butyrate on ameliorating small intestines damage caused by SD. The questionnaire survey of 534 college students showed that among 85.39% of the students who sleep less than 7h, 41.76% were suffering from

various bowel disorders. Furthermore, the author observed that butyrate supplementation markedly reversed sleep-deprivation-induced small intestinal mucosal injury in mice. The author focused on revealing the influence of insufficient sleep on the intestinal microbiota and its metabolites and further revealed the ameliorative effect of butyrate on sleep deprivation-induced small intestinal mucosal damages in human and mice.

The histone deacetylase inhibitor sodium butyrate exerts antidepressant-like effects in the mouse

Schroeder., *et al*. [8] investigated whether the histone deacetylase inhibitor sodium butyrate (SB) administrated of as single drug or in combination with the selective serotonin reuptake inhibitor (SSRI) fluoxetine exerts antidepressant-like effect in mice. SB exerts antidepressant-like effects in the mice (C57B/6J). The therapeutic benefits and molecular actions of histone modifying drugs, including co-treatment with SSRIs, and other newer generation antidepressant medications, warrant further exploration in experimental models.

Aging results in chronic systemic inflammation that can alter neuroinflammation of the brain

Matt., *et al*. [9] demonstrated that butyrate can attenuate pro-inflammatory cytokine expression in microglia in aged mice. Adult and aged mice were fed either a 1% cellulose (lower fiber) or 5% inulin (higher fiber) diet for 4 weeks. Findings indicated that mice fed inulin had an altered gut microbiome and increased butyrate, acetate, and total short chain fatty acid production. In addition, histological scoring of the distal colon demonstrated that aged animals on the low fiber diet had increased inflammatory infiltrate that was significantly reduced in animals consuming the high fiber diet. Furthermore, gene expression of inflammatory makers, epigenetic regulators, and the microglial sensor apparatus were altered by both diet and age, with aged animals exhibiting a more anti-inflammatory microglial profile on the high fiber diet. Thus, high fiber supplementation in aging is a non-invasive strategy to increase butyrate levels, and these data suggested that an increase in butyrate through added soluble fiber such as inulin could counterbalance the age-related microbiota dysbiosis, potentially leading to neurological benefits.

Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations

There is a growing recognition of the involvement of the gastrointestinal microbiota in the regulation of physiology and behavior. Microbiota-derived metabolites play a central role in the regulation of physiology and behavior. van de Wouw., *et al*. [10] investigated that microbiota-derived metabolites play a central role in the communication between microbes and their host, with short chain fatty acids (SCFAs) being perhaps the most studied. SCFAs are primarily derived from fermentation of dietary fibers and play a pivotal role in host gut, metabolic and immune function. All these factors have previously been demonstrated to be adversely affected by stress. Therefore, the author sought to assess whether SCFAs supplementation could counteract the enduring effects of the chronic psychosocial stress, C57BL/6J male mice received oral supplementation of a mixture of the three principle SCFAs (acetate, propionate and butyrate). One week later, mice underwent 3 weeks of repeated psychosocial stress followed by a comprehensive behavioral analysis. The author showed that SCFAs supplementation alleviates selective and enduring alterations induced by repeated psychosocial stress.

Butyric acid lowers arterial blood pressure via colon-vagus nerve signaling and GPR41/43 receptors

Onyszkiewicz., *et al*. [11] hypothesized the colon-derived butyric acid may affect hemodynamics arterial blood pressure and heart rate were recorded in anesthetized, male, 14-week-old Wister rats. A vehicle, butyric acid or 3-hydroxybutyrate, an antagonist of short chain fatty acid receptors of GPR41/43 were administered intravenously or into the colon. The author concluded that an increase in the concentration of butyric acid in the colon produced a significant hypotensive effect which dependents on the afferent colonic vagus nerve signaling and GPR41/43 receptors. Butyric acid seems to be one of mediators between gut microbiota and circulatory system.

Role of the gut microbiome in obstructive sleep apnea-induced hypertension

Durgan., *et al*. [12] tested the hypothesis that gut dysbiosis contributes to hypertension observed with obstructive sleep apnea (OSA). OSA was modeled in rats by inflating a tracheal balloon during the sleep cycle (10-s inflations, 60 per hour). On normal chow diet, OSA

had no effect on blood pressure, however, in rats fed a high-fat diet, blood pressure increased 24 and 29 mm Hg after 7 and 14 days of OSA, respectively. Bacterial community characterization was performed on fecal pellets isolated before and after 14 days of OSA in chow and high-fat fed rats. High-fat diet and OSA led to alterations of the gut microbiota, including decreases in bacterial taxa known to produce the short chain fatty acid butyric acid. The results demonstrated a causal relationship between gut dysbiosis and hypertension, and suggested that manipulation of the microbiota may be a viable treatment for OSA-induced, and possibly other forms of hypertension.

Discussion

Sleep-inducing drug is one of the most commercialized OTC-drugs in market. Many of the patients have difficulty of initiation of sleep with safer and more effective agent. Sleep-inducing drug is a one of the most commercialized drugs in market, and the medicines that are easily prescribed and can't be stopped. Thus, the insomnia patients triggered by taking sleep-induction pills at first, then administered several drugs, such as anti-depressant, and anti-psychiatric agent. In previous report the author showed that Kampo-medicine, Yokukan-san with Aloe vera juice (AVJ) as an adjuvant exhibited possible efficacy for modulation in brain homeostasis. The drug privation with AVJ provided health maintenance in patient with Hashimoto-disease clinical history and well-being QOL [13]. The present article suggested that the Kampo-drug; Kamishyoyo-san and the OTC drugs mitigate with AVJ as an adjuvant mitigate the improvement of sleep induction in case report 1-4. And an 80-years old-male patient had sleep induction drug and obstructive sleep apnea-induced hypertension drug in his ill history, had well-being with the drug without the sleep-induction drug and with AVJ as an adjuvant under walking-exercise in case report 5.

Summary

Butyrate can protect the brain and enhance plasticity in neurological disease models. Butyrate, neuro-epigenetics, prevents/treats brain disorders and improves brain health. Butyrate fermented with endophytic bacteria in Aloe vera gel plays a surprisingly big role in overall health, specially, optimal butyrate could level an increased duration of deep, non-rapid eye movement sleep and the sleep-inducing drugs in case report 1-5. Butyrate fermented in Aloe vera juice (AVJ) possibly prevents the taking polypharmacy of sleeping pills with participating as an adjuvant and shows the health benefit to get enough sleeping.

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