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Original article

Gut microbiota involved in sleep quality mediated by the gut-brain axis

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Abstract

Through the mediation of the gut-brain axis, sleep quality has a bidirectional effect on the gut microbiota. Using fecal T-RFLP flora analysis, we have found that improving sleep quality leads to changes in the gut microbiota. In particular, we observed an increase in short-chain fatty acid (SCFA)-producing bacteria such as *Bacteroidota*, *Oscillospiraceae*, and *Lachnospiraceae*. The microbiota of persons with poor "sleep quality" is similar to the pattern of dementia patients, and may approach the pattern of healthy people as "sleep quality" improves. In this report, we picked up major bacteria that are expected to be related to sleep quality and reviewed the literature. It seems important to avoid dysbiosis and maintain the dominance of SCFA-producing bacteria in order to maintain good "sleep quality" and hopefully prevent the progression of dementia.

***KEY WORDS*:** microbiota, sleep quality, dementia, short-chain fatty acids

Introduction

Six clinical trials have shown that various physical functions improve with improved sleep quality[1-6]. For PSQI-J, sleep quality improved significantly in all six trials, sleep onset time improved significantly in five out of six trials, sleep duration improved significantly in four out of six trials, and difficulty waking during the day improved significantly in three out of six trials. The overall assessment PSQIG improved significantly in all six trials. For the third trial, a crossover study was conducted with a control group, but the improvement in the subject groups was similar[3]. Similar results were obtained in all six trials, showing that the improvement in subjective symptoms was highly reproducible and that the use of the test bedding improved "sleep quality."

In the fifth trial, the relationship between sleep quality, intestinal flora, and amyloid beta (Aβ) clearance index (Aβ40/42) was examined[5]. As a result, an increase in short-chain fatty acid (SCFA)-producing bacteria was observed in the gut microbiota, indicating the influence of the gut-brain axis (***Fig.1-a***). The Aβ40/42 of the subjects was significantly higher than that of healthy subjects, suggesting the possibility that Aβ clearance may be reduced in subjects with poor "sleep quality."

Saji et al. compared the gut microbiota of dementia patients and healthy subjects and reported that the healthy subjects had more short-chain fatty acid-producing bacteria (***Fig.1-b***)[7]. This is a very interesting example of brain-gut coupling.

In this study, we focused on gut bacteria related to dementia and sleep quality in these clinical trials[5,7] and summarized recent findings.

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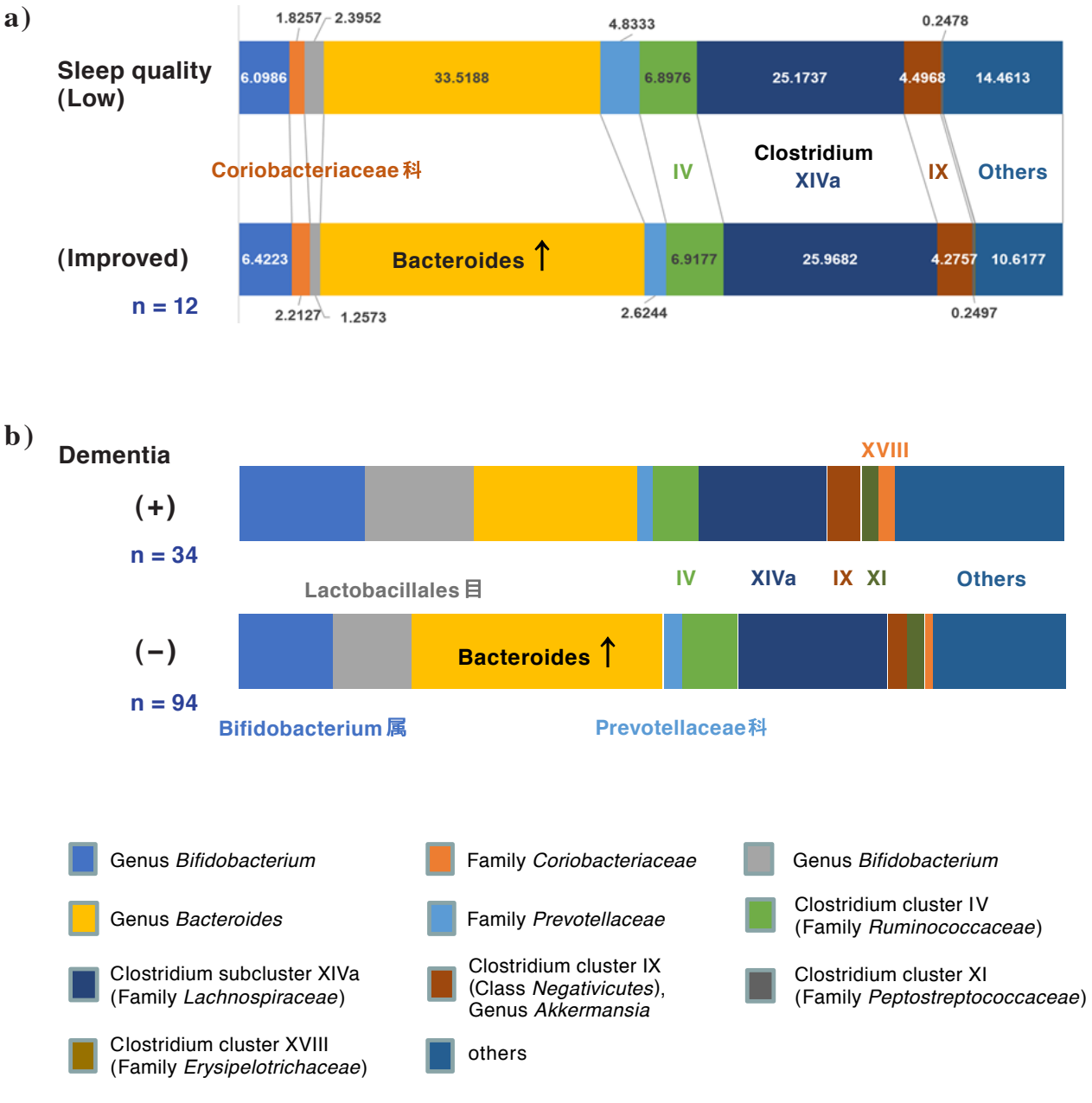

Fig. 1. **Comparison with other research findings.**

a) The gut microbiota of subjects with reduced "sleep quality". The microbiota composition shifted as "sleep quality" improved. **b)** The difference in microbiota composition between dementia patients and healthy subjects. Figure (**a**) quoted from Reference 5 and Figure (**b**) quoted and modified from Reference 7.

Methods

Gut microbiota

It is known that the human intestinal lumen is home to approximately 1,000 species and over 100 trillion intestinal bacteria that form a stable community (gut microbiota,) while forming a symbiotic and antagonistic relationship with each other. The bacteria that make up the gut microbiota interact with the host directly or through their metabolites, affecting our metabolic functions and immune system[8-11], and furthermore, bidirectionally affecting the central nervous system via the gut-brain axis[12,13].

Next-generation DNA sequencer technology is used to analyze the gut microbiota, and 16S rRNA amplicon analysis and shotgun whole metagenomic analysis are being performed. The 16S ribosomal RNA gene is said to be an essential gene for bacteria, and bacteria are classified based on the similarity of the base sequence. The unit obtained when the base sequence of the bacterial 16S ribosomal RNA gene is classified on a computer based on its similarity (generally 96-97%) is called an OTU (operational taxonomic unit). The number of OTUs represents the number of bacterial species that compose the bacterial flora, and the number of reads belonging to the same OTU is thought to represent the relative abundance of that species.

In this study, the major taxonomic groups of the human intestinal flora (*Bifidobacterium*, *Bacteroides*, etc.) were analyzed as OTUs. Bacteria related to those previously reported[5,7] were selected and a literature review was added.

Results

Changes in the intestinal flora

In fecal T-RFLP flora analysis, the proportion of *Bacteroides* genus bacteria was 33.5 ± 8.2% before use and 39.4 ± 7.3% after 8 weeks of use, showing a significant increase after 8 weeks compared to before use ($p < 0.001$, ***Fig. 1-a***)[5]. In addition to *Bacteroides*, an increase in SCFA-producing bacteria such as *Oscillospiraceae* and *Lachnospiraceae* was also observed. Analysis of other bacteria seems necessary. The importance of major bacteria to health is summarized below.

Genus Caproicibacter

Belonging to the family *Oscillospiraceae,* the genus *Caproicibacter* is comprised of a single known species, *Caproicibacter fermentans*, first described in 2020[14] after isolation from a gas bioreactor in Germany. *C. fermentans* is an obligate anaerobic, spore-forming bacterium with a gram positive-like cell wall structure despite staining gram-negative. Little is known of *C. fermentans* ecological role in the gut microbiome or its effects on human health.

C. fermentans is capable of metabolizing a variety of saccharides, including glucose, fructose, and sucrose. As metabolic byproducts, the bacterium produces SCFAs acetate, butyrate, and lactase, as well as the medium chain fatty acid caproate, ethanol, CO_2, and H_2.

The physiological significance of this bacterium is unclear.

Genus Lachnospiraceae incertae sedis

Lachnospiraceae incertae sedis, as the name states, is a taxon which contains bacteria of uncertain phylogeny and lacking description within the family *Lachnospiraceae*. The taxon contains an abundance of candidate species which have been genetically identified[15] but have not reportedly been cultured and lack a detailed metabolic description. Nevertheless, modern genomic techniques have allowed the detection of *L. incertae* sedis in a variety of contexts.

The taxon is reported to be abundant in those in better cardiovascular health[16] and in those without Crohn's disease[17]. Loss of *L. incertae sedis* may also serve as a biomarker for hepatocellular carcinoma, as it is significantly reduced in mouse models of the disease[18]. On the other hand, *L. incertae sedis* is enriched in non-alcoholic fatty liver disease[19], type 2 diabetes[20], alopecia areata[21], and is associated with major depressive disorder[22,23]. In infants, the taxon is more abundant with eczema[24] and correlated with lower mental development index scores[25]. As uncertain as its taxonomy, the observed relationship with human health is also unclear, revealing potentially both beneficial and pathogenic relationships.

The relationship with human health is still unclear, and since there is a possibility of both beneficial and pathogenic relationships, it is difficult to evaluate the physiological significance. However, these bacteria produce butyric acid and are known to be common in long-lived people[26], thus an increase in this taxon may be considered a positive effect. It is likely that the contradictory positive and negative health correlations with this taxon may be due to disparate effects of individual member species which are still awaiting an agreed upon taxonomic classification.

Genus Aminipila

Aminipila is a recently discovered genus, first described in 2018[27] when the type species *Aminipila butyrica* was isolated from a cattle waste bioreactor in Japan. Subsequently, two more species, *Aminipila terrae*[28] and *Aminipila luticellarii*[29], have been named. Information regarding the role of *Aminipila* in the gut microbiome remains sparse. *A. butyrica* is a strictly anaerobic gram-positive microbe. The species is asaccharolytic, relying on the fermentation of amino acids arginine, lysine, and serine as a growth substrate, producing the SCFAs acetate and butyrate as well as hydrogen sulfide as metabolic byproducts.

In humans, *A. butyrica* has been detected in the subgingival microbiome where its abundance may serve as a biomarker for rheumatoid arthritis[30]. However, experimental evidence of its role in the gut is lacking. *A. butyrica* has also been identified in the gut of sheep, where it promotes resistance to parasitic infection by helminth[31].

This bacterium may be beneficial in that it increases SCFA production and provides resistance to parasitic infections.

Genus Butyricimonas

Butyricimonas are a genus of obligate anaerobic gram-negative bacteria named for producing large amounts of butyric and isobutyric acid[32], and first isolated from rat fecal samples[33]. Metabolizing glucose, the major metabolic SCFA

endproducts are butyrate, isobutyrate, and isovalerate, with smaller amounts of acetate, propionate, and succinate [34]. The genus contains species such B. faecalis, *B. faecihominis*, *B. paravirosa*, *B. synergistica*, and *B. virosa*.

Butyricimonas is characterized by beneficial bacteria that perform and important function in SCFA production and the maintenance of intestinal homeostasis. As a significant butyrate producer, *Butyricimonas* contributes to maintaining intestinal barrier function and reduces inflammation. In mouse models of diabetes [35] and metabolic syndrome [36], ameliorating treatment was associated with enrichment of *Butyricimonas* and improvement of intestinal dysbiosis (e.g., increased SCFAs and reduced inflammation, intestinal barrier function, serum LPS). Furthermore, intake of *B. virosa* has demonstrated a protective effect against high fat diet induced diabetes in mice [37]. Additionally, in menopausal women increased intestinal production of SCFA butyrate was associated with increased muscle mass and abundance of B. virosa [38].

Butyricimonas abundance is associated with reduced BMI, and it is reduced by diets high in animal protein, saturated fats, and simple sugars [39]. In the successful treatment of chronic constipation with fecal microbiota transplant, *Butyricimonas* was significantly enriched in abundance after treatment [40].

Butyricimonas may also influence immune regulation and inflammation, as it is significantly reduced in multiple sclerosis patients, both with and without treatment, compared to healthy controls and its abundance is negatively correlated with proinflammatory gene expression characteristic of MS [41]. *Butyricimonas* is similarly reduced in patients with histamine intolerance [42], associated with an inflammatory intestinal reaction in response to intake of foods containing histamine. *Butyricimonas* is also significantly reduced in Cystic Fibrosis, and its abundance negatively correlated with gene expression associated with colorectal cancer [43].

An increase in these butyric acid-producing bacteria can be seen as a favorable change.

Genus Hydrogenoanaerobacterium

The genus *Hydrogenoanaerobacterium* contains a single known species, *H. saccharovorans*. The bacterium is an obligate anaerobic gram-negative microbe that was initially isolated form a hydrogen producing bioreactor in China [44]. As the name suggests, *H. saccharovorans* is supported by metabolizing a wide range of saccharides. The main endproducts of its glucose metabolism are ethanol, acetate, hydrogen, and carbon dioxide. *Hydrogenoanaerobacterium* has been detected as a member of the human gut microbiome in several studies, although the implications of *H. saccharovorans* for human health remains unclear, with most of the current data extracted from animal experimentation using mice.

In a mouse model of high fat diet induced obesity, oolong tea extract reduced weight gain and ameliorated lipid metabolism; *Hydrogenoanaerobacterium* was significantly enriched in the treatment group [45]. In mouse model of alcoholic liver, ameliorating treatment with a fungal extract resulted in increased abundance of *Hydrogenoanaerobacterium*, among other taxa [46]. Conversely, it has also been reported that *Hydrogenoanaerobacterium* is elevated in high fat diet-fed mice, and was reduced by treatment with resveratrol vie repression of mTOR Complex 2 [47].

With human data, the associations are notably more negative. *Hydrogenoanaerobacterium* abundance was observed to be significantly increased in sporadic Parkinson's Disorder patients [48] and in patients with both kidney stones and consuming a high nephrolithiasis risk diet [49]. In a study examining the use of fasting as a treatment for high blood pressure in metabolic syndrome patients, *Hydrogenoanaerobacterium* was one of several taxa enriched in patients whose blood pressure was non-responsive to treatment [50]. However, the current state of the literature is largely comprised of simple correlational data with little in the way of mechanistic understanding of the impact of *Hydrogenoanaerobacterium* on host health.

Looking at the human clinical data, this bacterium seems to be viewed negatively. The decrease in this bacterium may be a positive effect.

Genus Parasutterella

Parasutterella is an obligately anaerobic gram-negative genus and the most frequently reported taxa of *Betaproteobacteria* in the human gut, primarily represented by the species *P. excrementihominis* [51]. *P. excrementihominis* is asaccharolytic, primarily utilizing amino acids for energy metabolism. The bacterium plays a role in bile acid maintenance and cholesterol metabolism. It produces intermediate metabolites such as bile acid derivatives and succinate, which are utilized by other microbes in the gut.

Parasutterella shows numerous beneficial health effects as a symbiotic member of the gut microbiome. *Parasutterella* is significantly reduced by *C. difficile* carriage [52], and is enriched in patients for whom fecal microbiota transplant successfully treated recurring *C. difficile* infection [53]. *Parasutterella* abundance is negatively correlated with clinical indicators of obesity and metabolic disorder, such as BMI and blood glucose level [46, 54] and abundance is correlated with a reduction of serum lipids [55]. *Parasutterella* also appears to provide resistance against liver and kidney disease. In a mouse model of alcohol induced liver disease, microbiome transplants from alcoholic patients with and without hepatitis conferred susceptibility or resistance to liver damage, with *Parasutterella* the dominant genus of the hepatitis resistant group [56]. In patients with chronic kidney disease *Parasutterella* is significantly reduced compared to healthy controls, and its abundance is correlated with improved glomerular filtration rate and reduced levels of serum creatinine, blood urea nitrogen, and cystatin C [57]. During pregnancy, *P. excrementihominis* has neuroprotective effects on fetal development by increasing tryptophan metabolism in the gut and reducing kynurenine levels in maternal and fetal compartments [58]. *P. excrementihominis* is additionally enriched in healthy patients compared to those with pregnancy induced hypertension [59].

Despite its otherwise healthy presence/effects in the gut, *Parasutterella* is associated with inflammation in IBS [60], and is one of several enriched genera that are associated with autism spectrum disorder [61] and depression [62]. However, current data is conflicting. Despite its association with inflammation in IBS and colitis, a recent study found an increase of *Parasutterella* and other *Lachnospiraceae* genera and their SCFA products, chiefly butyrate, accompanied amelioration of ulcerative colitis [63]. It is possible that there

was a compensatory increase in *Parasutterella* in response to the presence of disease.

There exists controversy about the role of these bacteria. Nevertheless, we consider that the increase in these bacteria is an overall positive.

Genus Ruminococcus

Ruminococcus is a genus of anaerobic and gram-positive bacteria. *Ruminococcus* species abundance is positively correlated with SCFA production in the gut [64]: *R. albus* produces acetate from the breakdown of cellulose [65], *R. bromii* ferments acetate from resistant starches [66], and *R. gnavus* produces acetate, formate, lactate, and butyrate [67,68]. The health effects of *Ruminococcus* reported in the literature are mixed: the genus is enriched in type 2 diabetes [69], however it appears to have a protective effect against type 1 diabetes via promotion of CD8+ Treg cell proliferation in murine models [70]. Ultimately, the outcomes of *Ruminococcus* abundance are heavily dependent on species level relationships, although the weight of the literature leans toward negative health associations.

R. gnavus is frequently reported in a pathogenic context, being significantly enriched in obesity [71]. Distinguishable strains of *R. gnavus* are linked with inflammatory bowel disease, and blooms of the bacteria are associated with increased severity of symptoms [72,73]. *R. gnavus* also produces a pro-inflammatory polysaccharide that induces cytokine upregulation, and dysbiosis of the species has been reported in association with increased inflammation in Crohn's disease [74]. Further, *R. gnavus* overabundance has been associated with the development of respiratory allergic disease in infants [75], and mice fed *R. gnavus* develop histological signs of asthma [76]. Despite a generally negative influence on health, *R. gnavus* does have a positive effect in certain circumstances. It is reduced in infants with atopic dermatitis [77], and *R. gnavus* oral administration alleviates atopic dermatitis severity in a mouse model of the disease by modulating immune response and increasing butyrate production [78].

While *R. gnavus* is associated with Crohn's disease, other *Ruminococcus* species such as *R. albus*, *R. callidus*, and *R. bromii* are reduced in the disorder and are reported to be significantly more abundant in healthy controls [79].

Recent literature has tended to characterize this bacterium as unfavorable to health, but this point requires further investigation.

Phylum Pseudomonadota (Proteobacteria)

Pseudomonadota are a phylum of generally gram-negative bacteria, containing a highly diverse variety of bacterial species, including well-known genera *Escherichia*, *Salmonella*, and others. In contrast to the many obligate anaerobes found in the gut microbiome, there are numerous facultatively anaerobic species within *Pseudomonadota*. As such, *Pseudomonadota* are early colonizers of the gastrointestinal tract during infancy and facilitate the reshaping of the gut environment to better accommodate later colonization by depleting oxygen [80].

Pseudomonadota tend to be present at relatively low abundance [81] compared to *Bacillota* (*Firmicutes*) and *Bacteroidota*, however they are responsible for a significant amount of individual variation in functional genes of the gut microbiome [82]. While *Pseudomonadota* are commensal at low levels, when overabundant they can be a sign of intestinal dysbiosis [81] and are associated with disease states such as obesity [83], diabetes [84], Parkinson's [85], and cognitive decline [86,87].

Disorders involving elevated inflammation are also accompanied with *Pseudomonadota* dysbiosis. Respiratory diseases such as asthma involve dysbiosis of both the lung and gut microbiota, which is partially characterized by an overabundance of *Pseudomonadota* in both environments [88,89]. *Pseudomonadota* are significantly enriched while Bacillota are reduced in the gut of patients with irritable bowel syndrome [90,91]. Non-alcoholic Fatty Liver Disease is also associated with an elevated abundance of *Pseudomonadota* and microbial endotoxin production [92,93].

While large blooms of the phylum are dysbiotic and contribute to the pathogenesis of a wide range of illnesses, at relatively low levels of abundance the *Pseudomonadota* are a core member of the gut microbiota play a vital role in the initial bacterial colonization of the intestines. A diverse taxon, *Pseudomonadota* and contains beneficial as well as pathogenic organisms.

This bacterium is thought to play an important role in maintaining the homeostasis of the intestinal microflora, so having an excess or deficiency is not desirable. If the deficient bacteria increase and return to a healthy state, this can be considered a positive effect. If the excess bacteria are reduced to a healthy state, this would also be favorable.

Genus Mediterraneibacter

Mediterraneibacter is a genus of strictly anaerobic gram-positive bacteria, isolated from the fecal sample of an obese patient in France [94]. The type species is *M. massiliensis*, which produces acetate and isocaproate as the primary product of carbohydrate fermentation, while other species such as *M. butyricigenes* [95] produces butyrate. Other species include *M. hominis* [96], and reclassifications of *M. faecis* and *M. glycyrrhizinilyticus* from *Ruminococcus* and *Clostridium* respectively [94].

As a newly discovered genus, the role of *Mediterraneibacter* is still poorly understood. Early research indicates that it may be beneficial, as abundance of the genus is negatively correlated with severity of necrotic enteritis [97]. *M. faecis,* is a beneficial member of the gut microbiome, producing SCFAs [98,99] and thereby exerting antidiabetic [100] and anti-inflammatory effects [101].

Based on these findings, this increase in bacteria can be interpreted as a positive effect.

Genus Monoglobus

Monoglobus pectinilyticus is currently the only validly named species within the genus *Monoglobus*, isolated from a healthy human fecal sample in Korea [102]. *M. pectinilyticus* is a strictly anaerobic gram-positive bacterium characterized by its ability to ferment pectins, polysaccharides found in the walls of plant cells, which are abundant in citrus and other fruits. While unable to utilize glucose, the bacterium metabolizes fructose, producing the SCFAs acetate, formate, and lactate as metabolic byproducts.

Monoglobus appears to have a protective effect against liver disease. *Monoglobus* is significantly depleted in hepatitis B and hepatocellular carcinoma patients compared to healthy controls[103]. In children with biliary atresia, *Monoglobus* was significantly enriched in both patients who did not develop cholangitis after corrective surgery and in those whose jaundice cleared 6 months post-surgery[104]. *Monoglobus* is also correlated with Alzheimer's disease, being significantly reduced in AD patients compared to healthy controls: *Monoglobus* abundance was also negatively correlated with amyloid positivity[105] and blood triglyceride levels[106]. In patients with *C. difficile* infection, *Monoglobus* abundance was correlated with a reduction in infection severity and detectable *C. difficile* toxins[107].

The relative abundance of *Monoglobus* has been reported to be elevated in rheumatoid arthritis, and was correlated with CD4+ T cell counts and the levels of cytokines IL-2, IL-4, IL-10, TNF-α, and IFN-γ[108].

This increase in bacteria can be interpreted as a positive effect.

Genus Murimonas

The Genus *Murimonas* is comprised of a single species, *Murimonas* intestini, isolated from the mouse intestine[109]. *M. intestine* is an obligate anaerobic gram-positive bacterium in the family *Lachnospiraceae* that produces the SCFA acetate. While not much is yet known of the role of this bacterium in the ecology of the gut microbiome, *Murimonas* is reported to be significantly depleted in obesity compared to normal weight controls[110]. Additionally, *Murimonas* may influence the gut-brain axis in depression, as its abundance is reportedly correlated with increased levels of Brain Derived Neurotrophic Factor[111] and is reduced by chronic unpredictable stress induced depression in mouse models of depression[112].

M. intestini is an acetic acid-producing bacterium, and promotes BDNF production, which can be considered a positive effect.

Comparison with dementia patients and those with poor sleep quality

In previous reports, a notable characteristic of those without dementia[7] and those with improved "sleep quality"[5] was the marked increase in *Bacteroidota* (Genus *Bacteroides*), with an increase in *Oscillospiraceae* (Clostridium cluster IV (Family *Ruminococcaceae*)) and *Lachnospiraceae* (Clostridium subcluster XIVa (Family *Lachnospiraceae*)) (***Fig.1***). Sleep quality and intestinal flora are known to have bidirectional effects mediated by the gut-brain axis. Improving "sleep quality" may help escape the dementia pattern of bacterial flora disorders and transition to a non-dementia pattern.

Conclusion

Sleep quality and microbiota are closely linked by the gut-brain axis. In this report, we conducted a literature review of representative bacteria related to the gut-brain axis. It was suggested that improving sleep quality may increase SCFA-producing bacteria, which may help escape from dementia pattern dysbiosis and transition to a non-dementia pattern.

Conflict of interest declaration

None.

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