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CASE REPORT

Putative Role of Butyrate Fermented in Aloe vera gel for Depressive-like Behavior; Case Report: Remission of Depressive-like Behavior, Anemia, Fatigue and Cystitis

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ABSTRACT

The association between butyrate fermented in Aloe vera gel and neuro-epigenetics to modulate brain homeostasis was widely discussed. In case reports we demonstrated remission of depression, anemia and cystitis with the drug and Aloe vera juice ingestion, producing butyrate as an adjuvant. An increase in the abundance of beneficial bacteria and butyrogenic microbiota that contribute to age-dependent diseases such as depression-like behavior could be offer an effective strategy to target the debilitating ailments.

Key words: Butyrate fermented; Aloe vera gel juice; Modulation of depressive-like behavior; Case reports

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INTRODUCTION

Dietary manipulation of the gut microbiota composition may be a key variable in the diet-depression relationship. The role of the gut microbiota in dietary interventions for depression and anxiety was mediated by carbohydrate and fiber intake with the microbiota-mood associations. Butyrate one of short chain fatty acids (SCFAs) digested in the gut is an essential for maintaining a healthy environment in the gut. In the human colon, anaerobic bacteria such as *Clostridium butyricum*, *Roseburia intestinalis* and *Faeculibacterium prusnitzii* ferment carbohydrates and produce SCFAs; acetate, propionate and butyrate. In mitochondria of colon cells, 70-90% of butyrate is oxidized into acetate, which is then to generate large quantities of ATP, the primary form of cellular energy^[1].

There is emerging evidence that an unhealthy dietary pattern may increase the risk of developing depression or anxiety, whereas a healthy dietary pattern may decrease it. The recent research suggests that dietary interventions could help prevent or be an alternative or adjunct therapy for depression and anxiety. The gut microbiota is linked with the brain in a bidirectional relation, commonly termed the microbiome-gut-brain axis. The preclinical evidence suggests that the axis plays a key role in the regulation of brain function and behavior, such as autism spectrum disorder^[2]. In the present article we described the association between butyrate, neuro-epigenetics and gut microbiome to improve brain health. In three case reports we reported the improvement and remission of the depressive-like behavior with the drug and aloe vera juice ingestion as an adjuvant.

THE EFFECT OF SODIUM BUTYRATE ON SOCIAL BEHAVIOR AND REPETITIVE BEHAVIOR IN ANIMAL MODELS

Valvassori *et al.*^[3] evaluated the effects of sodium butyrate on depressive-like behavior and mitochondrial alteration parameters in animal models of depression induced by maternal deprivation or chronic mild stress in Wistar rats. Maternal depression was established by separating pups from their mothers for 3 h daily from postnatal day 1 to 10. Chronic mild stress was established by water deprivation, food deprivation, restraint stress, isolation, and flashing lights. Sodium butyrate or saline was administered twice a day for 7 days before the behavioral tests. Sodium butyrate treatment reversed maternal deprivation and chronic mild stress-induced dysfunction in the stratum of rats. Sodium butyrate showed antidepressant effects in maternal deprivation and chronic mild stress-treated rats, and this effect can be attributed to the action on the neurochemical pathways related to depression. Takuma *et al.*^[4] examined the effect of prenatal valproic acid (VPA) on cognitive function and whether the effect is improved by chronic treatment with VPA and sodium butyrate. The mice prenatally exposed to VPA showed a decrease in dendritic spine density in the hippocampal circuit region 1, and the spine loss was attenuated by chronic treatment with sodium butyrate or VPA. Acute treatment with sodium butyrate significantly increased acetylation of histone H3 in the hippocampus at 30 min, suggesting the difference in the mechanism for the effect of chronic VPA and sodium butyrate. Nankova *et al.*^[5] showed that short chain fatty acids (SCFAs) like propionic acid (PPA) and butyric acid (BA) administration to rodents over a variety of routes or developmental time periods can elicit behavioral, electrophysiological, neuropathological and biochemical effects consistent with findings in autism spectrum disorders (ASD) patients. PPA and BA induced broad alterations in gene expression including neurotransmitter systems, neuronal cell adhesion molecules, inflammation, oxidative stress, lipid metabolism and mitochondrial functions, all of which have been implicated in ASD. The effect of sodium butyrate (SB) on social behavior and repetitive behavior, and the frontal cortex transcriptome, was examined in the BTBR autism mouse model by Kratsman *et al.*^[6] Using RNA-sequencing analysis the author determined that the 100mg/kg dose of SB induced changes in many behavior-related genes in the prefrontal cortex, and particularly affected genes involved in neuronal excitation or inhibition. The decrease in several excitatory neurotransmitter and neuronal activating marker genes suggested that SB promotes the transcription of inhibitory pathway transcripts. SB increases social behaviors through modulation of the excitatory/inhibitory balance. Transcriptional modulation by SB may have beneficial effects on autism related behaviors.

CAN A HIGH FIBER DIET IMPROVE BRAIN HEALTH?

Butyrate has been extensively studied as a histone deacetylase inhibitor, but also functions as a ligand for a subset of G protein-coupled receptors and as an energy metabolite. These diverse modes of action make it well suited for solving the wide array of imbalances frequently encountered in neurological disorders. Bourassa *et al.*^[7] integrated evidence from the disparate fields of gastroenterology and neuroscience to hypothesize that the metabolism of a high fiber diet in the gut can alter gene expression in the brain to prevent neurodegeneration and promote regeneration. Grimaldi *et al.*^[8] assessed the influence of a prebiotic galacto-oligosaccharide

(B-GOS) on gut microbial ecology and metabolic function using fecal samples from autistic and non-autistic children in an in vitro gut model system. The microbiota of children with ASD contained a high number of *Clostridium* spp. and a lower number of *Bifidobacteria* compared with non-autistic children. B-GOS administration significantly increased *Bifidobacterial* populations in each compartment of the models, both with autistic and non-autistic-derived samples, and *Lactobacilli* in the final vessel of non-autistic models.

A POTENTIAL MECHANISM OF BUTYRATE FOR INTESTINE HOMEOSTASIS AND PROTECTION

Miao *et al.*^[9] have proved that the effect of sodium butyrate (SB) on the intestinal barrier function is mediated by activation of AMP-activated protein kinase (AMPK). Using the calcium switch assay in the Caco-2 cell monolayer model, the author found that SB activated AMPK mainly by increasing the calcium level via promoting store-operated calcium entry. Upon the activation of AMPK, SB promoted the reassembly of tight junctions based on reducing the phosphorylation of myosin II regulatory light chain at serine 19 and increasing phosphorylation of protein kinase C β 2 at serine 660. Inhibiting protein kinase C β blocked the reassembly of tight junctions induced by SB in the barrier monolayer model. The results suggested potential mechanism of SB for intestine homeostasis and protection.

ANTI-INFLAMMATORY ROLE OF SODIUM BUTYRATE FROM THE ASPECT OF MICROGLIAL PROCESS ELONGATION

Microglia is a kind of innate immune cells in nervous system which is in a ramified status with branched processes in normal condition. Wang *et al.*^[10] investigated the influence of sodium butyrate (SB) in the gut on microglial process. The results showed that SB induced reversible elongations of microglial process in both normal and inflammatory conditions, and these elongations were accompanied with significant changes in markers reflecting the pro-inflammatory and anti-inflammatory status of microglia. The protein kinase B (Akt)-RhoGTPase signal was considered to mediate the effect of SB on microglial process. Further analysis showed that incubation of microglia with two other histone deacetylase inhibitors (HDAC) trichostatin A and valproic acid also promoted microglial process elongation and Akt phosphorylation, suggesting that the SB-triggered microglial process elongation may be mediated by HDAC inhibition.

BUTYRATE ENHANCES MITOCHONDRIAL FUNCTION DURING OXIDATIVE STRESS IN CELL LINES FROM BOYS WITH AUTISM

Butyrate positively modulates mitochondrial function, including enhancing oxidative phosphorylation and β -oxidation and has been proposed as a neuro-protectant. Rose *et al.*^[11] developed a lymphoblastoid cell line (LCL) model of autism spectrum disorders (ASD), with a subset of LCLs demonstrating mitochondrial dysfunction (AD-A) and another subset of LCLs demonstrating normal mitochondrial function (AD-N). Given the positive modulation of butyrate on mitochondrial function, the author hypothesized that butyrate would have a preferential positive effect

on AD-A LCLs. To this end the author measured mitochondrial function in ASD and age-matched control LCLs, all derived from boys, following 24 and 48 h exposure to butyrate both with and without an *in vitro* increase in reactive oxygen species. The author examined the expression of key genes involved in cellular and mitochondrial response to stress. The data showed that the enteric microbiome-derived butyrate modulates mitochondrial activity, with this modulation dependent on concentration, microenvironment redox state, and the underlying mitochondrial function of the cell.

MODULATING THE GUT MICROBIOTA-PRODUCING BUTYRATE COULD BE A PROMISING STRATEGY FOR THE TREATMENT OF AUTISM SPECTRUM DISORDER

Cumulative evidence reveals that the gut microbiota and its metabolites, such as short chain fatty acids, play an important role in gastro intestinal disorders and the pathogenesis of autism. Liu *et al*^[12] found lower levels of fecal acetic acid and butyrate and higher level of fecal valeric acid in autism spectrum disorder (ASD) subjects. And the author identified decreased abundances of key butyrate producing taxa, *Ruminococcaceae*, *Eubacterium*, *Lachnospiraceae* and *Erysipelotrichaceae*, and an increased abundance of valeric acid associated bacteria among autistic individuals. Constipation was the only gastrointestinal disorder in ASD children. Modulating the gut microbiota, especially butyrate-producing bacteria, could be a promising strategy in the search for alternatives for the treatment of ASD.

TOLERABILITY OF PROBIOTIC/COLOSTRUM SUPPLEMENTATION ON GUT FUNCTION IN CHILDREN WITH AUTISM

The study objective by Sanctuary *et al*^[13] was to assess tolerability of a probiotic (*Bifidobacterium infantis*) in combination with a bovine colostrum product (BCP) as a source of prebiotic oligosaccharides and to evaluate gastrointestinal (GI), microbiome and immune factors in children with ASD and GI-comorbidities. The pilot study is randomized, double blind, controlled trial of combination treatment (BCP + *B. infantis*) vs. BCP alone in a cross-over study in children ages 2-11 with ASD and GI comorbidities ($n = 8$). This 12-week study included 5 weeks of probiotic-prebiotic supplementation, followed by a two-week washout period, and 5 weeks of prebiotic only supplementation. The results suggest that the combination treatment is well-tolerated in this cohort. The most common side effect was mild gassiness. Some participants on both treatments saw a reduction in the common frequency of certain GI symptoms, as well as reduced occurrence of particular aberrant behaviors.

RELATIONSHIPS AMONG DIET, THE GASTROINTESTINAL MICROBIOTA AND NEGATIVE EMOTIONAL STATES IN ADULTS

Taylor *et al*^[14] investigated the associations among diet, gastrointestinal (GI) microbiota, and mood in adults without mood disorders by conducting a cross-sectional examination of dietary intake, subjective emotional state, and fecal microbial taxa abundances. Adults ($N=133$; 25-45 years of age) without physician-diagnosed mood disorders were studied. The results suggested that GI microbes are related to mood in adults without diagnosed

mood disorders and that these relationships differ by sex and are influenced by dietary fiber intake. Incorporating dietary intake data in gut-microbiota-brain studies may help clarify the roles of specific microbes and dietary components in mental health symptoms.

COLONIZATION OF THE CAENORHABDITIS ELEGANS GUT WITH HUMAN ENTERIC BACTERIAL PATHOGENS LEADS TO PROTEOSTASIS DISRUPTION THAT IS RESCUED BY BUTYRATE

Numerous human diseases are associated with the chronic expression of misfolded and aggregation-prone proteins. Folding and unfolding are crucial ways of regulating biological activity and targeting proteins to different cellular locations. Walker *et al*^[15] investigated the effect of bacteria on host proteostasis. According to Gidalevitz *et al*^[16], Walker used *Caenorhabditis elegans* expressing tissue-specific polyglutamine reporters that defect changes in the protein holding environment. Walker^[15] found that colonization of the *C. elegans* gut with enteric bacterial pathogens disrupted proteostasis in the intestine, muscle, neurons and the gonad, while the presence of bacteria that conditionally synthesize butyrate, which is a beneficial molecule in neurodegenerative disease, suppressed aggregation and the association proteotoxicity. Co-colonization with these butyrogenic strain suppressed bacteria-induced protein aggregation, emphasizing the importance of microbial interaction and its impact on host proteostasis. Further experiments demonstrated that the beneficial effect of butyrate depended on the bacteria that colonized the gut and that this protection effect required SKN-1/Nrf2 and DAF-16/FOXO transcription factors. The author found bacteria-derived protein aggregates contribute to the observed distribution of host proteostasis. These results revealed the significance of enteric infection and gut dysbiosis on the pathogenesis of protein conformational disease and demonstrated the potential of using butyrate-producing microbes as a preventive and treatment strategy for neurodegenerative disease.

Bacteria-derived protein aggregates contribute to the disruption of host proteostasis

Neurodegenerative protein conformational diseases are characterized by the misfolding and aggregation of metastable protein encoded within the host genome. The study^[15] suggested that bacterial products contribute to the toxic aggregation of endogenous host proteins; bacteria-derived protein aggregates. Aggregation of misfolded proteins that escape the cellular quality-control mechanisms is a common feature of a wide range of highly debilitating and increasingly prevalent diseases. Walker *et al*^[17] refer to these products as bacteria-derived protein aggregate (BDPAs). The abundance and proteotoxicity of BDPAs are influenced by gentamicin, an aminoglycoside antibiotic that induces protein misfolding, and by butyrate, that the author previously found to affect host protein aggregation and the associated toxicity.

TARGETING THE HUMAN GUT MICROBIOTA AS A POTENTIAL PREVENTION, DETECTION, AND TREATMENT OF PROTEIN-CONFORMATIONAL DISEASES

Age-dependent protein-conformational diseases, such as Alzheimer's disease, Parkinson's disease, or amyotrophic lateral sclerosis (ALS),

are characterized by misfolding and aggregation of metastable proteins present within the proteome of the affected individual. Hertzberg *et al.*^[18] found that *Prevotella* abundance was lower in ALS patients, suggesting that this genus may provide protection against proteotoxicity. A recent study found *Prevotella* sp. that significantly suppressed polyglutamine protein aggregation in the *Caenorhabditis elegans* model^[15], suggesting that these specific species may enhance host proteostasis and protect the host against protein misfolding and aggregation. The protective effect of butyrate and butyrogenic bacteria, *Prevotella* spp. and possibly other microbes, such as *Bacillus subtilis* that was recently found to suppress aggregation of a α -synuclein in a Parkinson's disease *C. elegans* model (Goya *et al.*^[19]), will be likely open new opportunities for prevention, detection, and treatment of protein-conformational diseases. In preliminary report we identified following microbiota in Aloe vera leaf gel in which butyrate fermented was found: *Bacillus cereus*, *B. licheniformis*, and *Lactobacillus parafimmentarius*. Identification of butyrate-producing endophytic microbiota in Aloe vera gel fermentation and finding of anti-inflammatory as well as antioxidant activities of butyrate in the fermented gel may help explain the known beneficial effects of butyrate in intestinal colon and on colitis^[20].

THE ASD CHILDREN HARBOR AN ALTERED DEVELOPMENTAL PROFILE OF THE GUT MICROBIOTA DISTINCT FROM THAT OF TYPICALLY DEVELOPING CHILDREN

Wan *et al.*^[21] found the compositional and functional alterations in gut microbiome in association with age in children with ASD and to identify novel fecal bacterial markers for predicting ASD. The author performed deep metagenomics sequencing in fecal samples of 146 Chinese children (72 ASD and 74 typically developing (TD) children. Children with ASD had significant alterations in fecal microbiome composition compared with TD children characterized by increased bacterial richness and altered microbiome composition. High amount with areas under the receiver operating curve (AUC) of *Clostridium*, *Dialister* and *Coprobacillus* spp. and low amount with AUC of *Faecalibacterium* spp. were identified. Gut microbiome in Chinese children with ASD was altered in composition, ecological network and functionality compared with TD children. The author identified novel bacterial makers for prediction of ASD and demonstrated persistent underdevelopment of the gut microbiota in children with ASD which lagged behind their respective age-matched peers.

CASE REPORTS

Case report 1: Remission of depression with the drug and aloe vera juice (AVJ) ingestion

A 36-years old male who had job to IT-related-company after graduated university, had a hard work for one year. He administered hypnotic, sleeping and anti-depressant drugs three times per day at 23-years old. But he could not recover during the time of drug administration and took a leave of currently undergoing medical care at home on July, 2010. He retired the job on March, 2011. He decided to refusal of doctor's care and to ingest AVJ according to his friend's suggestion on December, 2012. Since then he has a well-being of QOL with AVJ supplementation and got a job.

Case report 2: Remission of anemia with the drug and AVJ ingestion

A~30 years old female who had gone on diet in her high school

day because of tendency to be obese, had become anemia in her university student time. When she get into insurance at the time of job, she could not obtain it because of suffer from anemia. Then she started to ingest AVJ by the recommendation of her friend. After 3 months ingestion of AVJ, she got into insurance and got a job.

Case report 3: Remission of cystitis with the drug and AVJ ingestion

A~58-years old female who had Hey-fever at 38-years old, took a long-term care of her parents for 13-years. She had a severe fatigue and heavy constipation, and started menopause at 49-years old and diagnosed anemia. On August, 2017 at 55 years-old, she diagnosed cystitis, showing the estimated glomerular filtration rate (eGFR) 48. She started the drug administration for one year, but the eGFR showed 56. Then she started to ingest aloe vera juice (AVJ) supplement with the drug on February, 2019. On October, 2021 at 59-year old, her eGFR showed 63.7 expressing a weak renal dysfunction. She remitted anemia, cystitis, heavy constipation and renal disorders with the drug and AVJ ingestion. She had well-being QOL on July, 2022.

SUMMARY

We discussed the current knowledge focusing on the influence of butyrate fermented in Aloe vera gel by which the gut-microbiota is beneficial for behavior to gut-brain homeostasis. In previous report we showed that long-term successive ingestion of aloe vera juice (AVJ) may help to modulate the immune-sensitive in a mitigation of pathogenesis and provide high concentration of butyrate-producing microbiome, *Faecalibacterium* spp. The role fermented butyrate on Alzheimer's disease and Parkinson's disease was discussed on the basis of gut microbiota-brain axis^[22]. In case reports we demonstrated remission of depression, anemia and cystitis with the drug and AVJ-producing butyrate as an adjuvant.

An increase in the abundance of beneficial bacteria, and butyrogenic microbiota could offer an effective strategy to target the debilitating ailments. The intestinal butyrogenic microbiota may be a potential theranostic tool for personalized medicine. Recently it is becoming more evident that healthcare will expand into personalized medicine to provide intervention strategies that modify individual gut microbiota.

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