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REVIEW

## Beneficial Efficacy of Histone Deacetylase Inhibitor, Butyrate on the Development of Epilepsy in Childhood; Case Reports; Epilepsy Treatment With the Medicine and Aloe Vera Juice as an Adjuvant

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### ABSTRACT

Possible prophylaxes of histone deacetylase inhibitor butyrate fermented in Aloe vera gel were discussed on the brain histone acetylation and reduction of phenolic metabolites in autism spectrum disorder (ASD) and epilepsy patients in childhood. In case reports of ASD patient and epilepsy children, the improvement with the medicine and adjuvant use of aloe vera juice (AVJ) was clearly exhibited. In case reports 1-3 the efficacy of the drug with aloe AVJ as an adjuvant to ASD patient and epileptic children was demonstrated

and the improvement of gut intestinal ecology in the patients was suggested. Case report 2 and 3 strongly expressed the importance of balance between the intestinal ecology and the developmental body in childhood on the medicinal care of epilepsy.

**Key words:** Histone deacetylase inhibitor; Butyrate; Suppression; Autism spectrum disorders; Childhood epilepsy

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### INTRODUCTION

Histone deacetylase (HDACs) are a family of proteins involved in both physiological and pathological conditions by regulating the status of chromatin histone acetylation. Epigenetic mechanisms, such as alterations in histone acetylation based on histone deacetylases (HDACs) activity, have been linked to several brain disorders including epilepsy and the epileptogenic process. Citraro et al<sup>[1]</sup> investigated the effects of two HDAC inhibitors (HDACI), sodium butyrate and valproic acid and their co-administration on development of absence seizures and related psychiatric/neurologic comorbidities following two different experimental paradigms in WAG/Rij rats. The author suggested that histone modification may have a crucial role in the development of epilepsy and early treatment with HDACI might be a possible strategy for preventing epileptogenesis also affecting behavioral comorbidity. Epigenetic mechanisms are involved in epilepsy and chronic pain development, indicating HDACIs as potential therapeutic agents for the development of human epilepsy. De Caro et al<sup>[2]</sup> investigated the effects of the natural HDACI, sodium butyrate in comparison with valproic acid (VPA) in a validated genetic model of generalized absence epilepsy and epileptogenesis in WAG/Rij rats. WAG/Rij

rats were treated with butyrate, VPA and their combination daily *per os* for 6 months. WAG/Rij rats showed an altered pain threshold throughout the study. Butyrate and butyrate+VPA decreased the expression of NFκB and enhanced glutathione reductase; protein oxidation was reduced. Butyrate alone or in co-administration with VPA, is a valuable candidate for managing the epilepsy-related persistence pain.

In the present review we describe the relationship between the microbiota gut-brain axis and the development of epilepsy and Case reports: Epilepsy treatment with the medicine and aloe vera juice as an adjuvant in childhood.

## KETOGENIC DIET (KD) CAN ALTER THE COMPOSITION OF INTESTINAL MICROBIOTA IN CHILDREN WITH REFRACTORY EPILEPSY

Ketogenic diet (KD) therapies are widely used treatments for epilepsy, but the factors influencing their responsiveness remain unknown. The KD involves eating high-fat foods with moderate amounts of proteins and a low amount of carbohydrates. This diet tricks the body into burning fats and ketones over carbohydrate. Mackay *et al*<sup>[3]</sup> reported efficacy and tolerability of the KD in refractory pediatric epilepsy. Median age at initiation of the KD was 6.1 years. Median duration of the treatment was 9 months. Twenty-Six consecutive children were treated with the classical KD from 1996 to 2021. The epilepsy syndromes included symptomatic generalized epilepsy, idiopathic generalized epilepsy, symptomatic partial epilepsy and unclassified epilepsy. One child was lost to follow up. Twelve children (46%) were treated for >12 months; one still remains on the KD. Four children (16%) became seizure-free. Five children (20%) had 50-99% reduction in seizures, seven (28%) had < 50% reduction in seizures and eight (36%) had no improvement. In conclusion, the KD is an effective treatment for some children with refractory epilepsy, being generally well tolerated and rarely associated with side-effects. Response is not necessarily predicted by age, syndrome or etiology.

### Altered gut microbiome composition in children with refractory epilepsy

Zhang *et al*<sup>[4]</sup> analyzed 20 patients (14 males, 6 females) treated with KD. Clinical efficacy, electroencephalogram (EEG) changes, and laboratory tests were evaluated, and fecal specimens were obtained prior to and 6 months after therapy. After 6 months of treatment, 2 patients were seizure free, 3 had ≥90% seizure reduction, 5 had a reduction of 50-89%, and 10 had <50% reduction. All 10 responders showed an improvement in EEG. Compared with baseline, fecal microbial profiles showed lower alpha diversity after KD therapy and revealed significantly decreased abundance of *Firmicutes* and increased levels of *Bacteroidetes*.

### The association with fecal short chain acid (SCFA) in children with drug refractory epilepsy (DRE) before and after treatment with a ketogenic diet (KD)

Gong *et al*<sup>[5]</sup> conducted a cross-sectional study of 12 children with DRE and 12 matched healthy controls to compare the changes in fecal microbiomes and SCFAs. A higher microbiota alpha diversity and a significant increase in *Actinobacteria* at the phylum level and *Enterococcus*, *Anaerostipes*, *Bifidobacterium*, *Bacteroides* and *Blautia* at the genus level were observed in the children with DRE.

A significant correlation was observed between the changes in the microbiome genera after KD treatment. The SCFAs content in the fecal after 6 months of KD treatment increased and was highly correlated with the gut bacteria.

### Modulation of PPAR-γ could be a potential treatment for epileptic seizures and regulation of brain PPAR-γ 2 contributing to ketogenic diet anti-seizure efficacy

The peroxisome proliferator-activated receptor (PPAR) family, type 2 nucleus receptors have been successively tested for their neuroprotective potential in certain central nervous system diseases. Hung *et al*<sup>[6]</sup> determined if modulation by PPAR-γ could attenuate pilocarpine-induced seizures and decrease neuronal excitability, using adult male *C57BL/6* mice: one group received pretreatment with pioglitazone (a PPAR-γ agonist) and the other received dimethyl sulfoxide for a period of 2 weeks.

In conclusion, PPAR-γ deficiency aggravated neuronal excitability and excitotoxicity. PPAR-γ attenuated pilocarpine-induced seizure severity, neuronal loss, blood brain barrier damage, and sodium currents in hippocampal neurons. Modulation of PPAR-γ could be a potential novel treatment for epileptic seizure. Simeone *et al*<sup>[7]</sup> examined whether PPAR-γ contributes to the anti-seizure efficacy of the KD. The author found that the KD increased nuclear protein content of the PPAR-γ2 splice variants by 2-4 fold in brain homogenates from wild-type and epileptic *Kv1.1* knockout mice (KO). And administrating the PPAR-γ2 agonist pioglitazone increased PPAR-γ2 expression by 2-fold and reduced seizures in *Kv1.1*KO mice by ~80%. The findings implicated brain PPAR-γ2 among the mechanisms by which the KD reduces seizures and strongly support the development of PPAR-γ2 as a therapeutic target for severe, refractory epilepsy.

### Aloe vera phytosterols activate PPAR transcription in vitro.

Aloe vera minor phytosterols, lophenol (Lo) and cycloartenol (Cy), were shown as anti-diabetic compounds in a type 2 diabetic model animal. Nomaguchi *et al*<sup>[8]</sup> investigated the effects of Lo and Cy on PPAR using a luciferase reporter assay. The author confirmed that aloe phytosterols activate PPAR transcription in vitro. The aloe vera phytosterols activated PPAR in a dose-dependent manner. The expression levels of many PPAR target genes were changed in the aloe vera phytosterols compared with those in the control high-fat diet group. And the quantitative gene expression analysis in diet-induced obesity mice model, suggested that aloe vera phytosterols improve fatty acid metabolism in the liver and act as ligand for PPAR and improve the expression levels of PPAR target genes in the livers of mice with diet-induced obesity.

## FECAL MICROBIOTA TRANSPLANTATION FOR EPILEPSY

Fecal microbiota transplantation (FMT) is a promising strategy that involves reconstruction of gut microbiota. It has been considered as a treatment of Crohn's disease (CD) and certain neurological diseases. He *et al*<sup>[9]</sup> reported the case report that used FMT to achieve remission of intestinal and neurological symptoms in a girl with CD and a 17-years history of epilepsy. During 20 months of follow-up, FMT has proved its efficacy in preventing relapse of seizures after withdrawing the antiepileptic drugs. Furthermore, this finding highlighted the role of microbiota-gut-brain axis and inspired a novel treatment for epilepsy through remodeling gut microbiota.

## ADMINISTRATION OF PROBIOTICS AS A SUPPLEMENTARY TREATMENT IN DRUG-RESISTANCE EPILEPSY

Epilepsy is a neurological disease with high global prevalence. Despite the range of drug-based treatments currently available to control the condition, one in 3 patients experiences epileptic seizures. Gomez-Eguilaz *et al*<sup>[10]</sup> investigated the effectiveness of probiotics for controlling epileptic seizures in patients with drug-resistant epilepsy. Forty-five patients with drug-resistant epilepsy were administered a probiotics mixture (*Streptococcus thermophilus*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracaesei*, *L. delbrueckii*, *subsp. bulgaricus*, *Bifidobacterium breve*, *B. longus*, *B. infantis*) for 4 months. Patients were assessed before and after taking the probiotics. The author found that probiotics may be an option for supplementary therapy. Since the use of the probiotics mixture is safe both during and after supplementation, they may contribute to improving seizure control, and therefore quality of life, in patients with drug-resistant epilepsy. The study has been registered: NCT03403907.

## THE POTENTIAL ROLE OF HISTONE DEACETYLASE INHIBITOR BUTYRATE TO PREVENT THE DEVELOPMENT AND PERSISTENCE OF TEMPORAL LOBE EPILEPSY

Epilepsy is a common brain disease characterized by repeated unprovoked seizures. Temporal lobe epilepsy (TLE) is caused by diverse precipitating factors such as brain injury. Reddy *et al*<sup>[11]</sup> reported a novel role of histone deacetylation as a critical epigenetic mechanism in epileptogenesis.

Experiments were conducted using daily treatment with histone deacetylase inhibitor (HDACi), butyrate, in the hippocampus kindling model of TLE, a classic model heavily used to approve drugs for treatment of epilepsy. HDAC inhibition showed erasure of the epileptogenic state in epileptic animals. Butyrate-treated wild type mice exhibited a powerful reduction in mossy fiber sprouting, a morphologic index of epileptogenesis. HDAC inhibition prevents the development of TLE, indicating HDAC's critical signaling role in epileptogenesis.

## HISTONE ACETYLATION CHANGES ARE ASSOCIATED WITH EPILEPSY; EPIGENETIC CHANGES CONTRIBUTE TO EPILEPSY DEVELOPMENT

Boison *et al*<sup>[12]</sup> discussed adenosine biochemistry as a novel therapeutic strategy to reconstruct the DNA methylome as antiepileptogenic strategy as well as metabolic mediators, such as  $\beta$ -hydroxybutyrate, which affect histone acetylation. Clinical and experimental evidence demonstrated that epilepsy and its progression can be prevented by metabolic and biochemical manipulations that target previously unrecognized epigenetic functions controlling to epilepsy development and maintenance of the epileptic state. Deutsch *et al*<sup>[13]</sup> reported that sodium butyrate, a centrally-active histone deacetylase inhibitor that promotes gene expression, was shown to modulate the stress-induced reduction of the ability of dizocilpine, a noncompetitive N-methyl- D-aspartate receptor antagonist, to antagonize electrically-precipitated seizures. The author extended the

work to look at sodium butyrate's modulatory effect on stress-induced changes in the anti-seizure efficacy of flurazepam, a benzodiazepine receptor agonist, in two strains of mice. Epigenetic mechanisms, genetic strain differences and a standard stress interacted to alter flurazepam's anti-seizure efficacy. The data supported examination and development of epigenetic treatment strategies.

## EXOGENOUS AND ENDOGENOUS HDAC INHIBITOR EFFECTS IN RUBINSTEIN-TAYBI SYNDROME MODELS

Rubinstein-Taybi syndrome (RSTS) is an autosomal dominant disorder with specific signs and neurodevelopmental impairment. The two known proteins altered in the majority of RSTS patients are the histone acetylation regulators CBP and p300. The transcription coactivators; cAMP response element binding protein (CBP) and p300 are highly homologous acetyltransferases that mediate histone 3: lysine 27 acetylation (H3K27ac) at regulatory elements such as enhancers and promoters. For assessing possible ameliorative effect of exogenous and endogenous HDAC inhibitors (HDACi), Di Fede *et al*<sup>[14]</sup> exploited *in vivo* and *in vitro* RSTS models. HDACi effects were tested on *Drosophila melanogaster*, showing molecular rescue. In the same model the author observed a shift in gut microbiota composition. Then the author observed a significant depletion in butyrate-producing bacteria in RSTS patients. The study showed the possibility of modulating acetylation equilibrium by HDACi treatments and the importance of microbiota composition in a chromatinopathy.

## POLYSACCHARIDES AS POTENTIAL AGENT FOR TREATMENT OF EPILEPSY

The beneficial effects of polysaccharides from Chinese medicines for treatment of epilepsy include regulation of inflammatory factors, neurotransmitters, ion channels and antioxidant reactions. Polysaccharides could be digested by intestinal microbial flora, referred as "intestinal brain organ" or "adult's second brain", may be the target for treatment of epilepsy. Actually, polysaccharides can effectively improve the type and quantity of intestinal flora such as *Bifidobacteria* and lactic acid bacteria and achieve the purpose of treating epilepsy. Xie *et al*<sup>[15]</sup> discussed polysaccharides as next potential agent to ketogenic diet for the treatment of epilepsy.

## ADHERENCE TO THE MEDITERRANEAN DIET IN CHILDREN WITH EPILEPSY

The Mediterranean diet (MD) focuses on plant-based foods, fresh fruits and vegetables, and eating lean proteins. This diet shifts the emphasis away from processed foods and is considered more of a way of eating than a traditional diet. The cross-sectional studies by Kaner *et al*<sup>[16]</sup> was carried out with a total of 85 children aged 2-18 years and their parents who attended the outpatient pediatric neurology clinic of a university hospital. Adherence to the MD was assessed using the MD Quality (KIDMED) index. A positive and statistically significant relationship was found between the children's KIDMED index score and carbohydrate, fiber, soluble fiber, iron, potassium, calcium and magnesium values. Majority of children diagnosed with epilepsy had moderate adherence to the MD, and that the KIDMED index might be used in the evaluation of healthy eating habits in children diagnosed with epilepsy. Diet quality should be improved in children with epilepsy.

## A ROLE OF ORAL SMALL-MOLECULE METABOLITES FOR THE GASTROINTESTINAL (GI) TRACT OR MICROBIOME IN ADOLESCENTS AUTISM SPECTRUM DISORDER (ASD)

ASD is defined by hallmark behaviors involving reduced communication and social interaction as well as repetitive activities and restricted interests. Gastrointestinal issues are common in ASD, and studies have identified changes in the gut microbiome of individuals with ASD compared to control populations. In the previous paper we reported that butyrate, a metabolite of short chain fatty acid, by the gut microbiota in large intestine contributes to impact on intestinal health and host well-being with its beneficial activity in inflammation and neurological disorders<sup>[17]</sup>. The gut microbiome has played a crucial role in the multi-directional gut-brain-axis that integrates the gut and central nerve system activities. However a role for the GI tract or microbiome in ASD remains controversial. Campbell *et al*<sup>[18,19]</sup> reported that an oral GI-restricted adsorbent (AB-2004) that has affinity for small aromatic or phenolic molecules relieves anxiety-like behaviors that are driven by a gut microbial metabolite in mice. And a pilot human study was designated and completed to evaluate the safety of AB-2004 in an open-label, single-cohort, and multiple-ascending-dose clinical trial enrolled 30 adolescents with ASD and GI symptoms in New Zealand and Australian. Significant reductions in specific urinary and plasma levels of gut bacterial metabolites, 4-ethylphenyl sulfate and p-cresol glucoside were observed between baseline and end of AB2004 treatment, demonstrating likely target engagement. The author observed improvements in multiple exploratory behavioral endpoints, most significantly in post-hoc analysis of anxiety and irritability, as well as GI health, after 8 weeks of treatment. The results (trial registration No.ACTR12618001856291) suggest that targeting gut-derived metabolites with an oral adsorbent is safe and well-tolerated approach to improving symptoms associated with ASD.

## THE NEUROPROTECTIVE EFFECT OF BUTYRATE AGAINST THE PENTYLENETETRAZOL (PTZ)-INDUCED KINDLING EPILEPSY

Li *et al*<sup>[20]</sup> investigated that seizure latency was effectively increased and the intensity of seizures decreased by treatment with sodium butyrate (SB). SB and sodium valproate (SV) for 40 days and PTZ injection every day were conducted for Kunming mice, to investigate seizure intensity and latency, oxidative stress parameters, mitochondrial structure and function, histopathology, and Keap1/Nrf2/HO-1 expressions. The results of a series of functional tests indicted a significant improvement of neurological function following SB treatment. In a mouse model of seizures, brain injury and neurological deficits can be attenuated by treatment with butyrate through the activation of Nrf2 pathway and the improvement of mitochondrial function. Seizure intensity was decreased and seizure latency was prolonged by SB. The Keap1/Nrf2/HO-1 signal pathway was associated with the neuroprotective influence of SB on the mice.

## CASE REPORTS

**Case report 1: Putative efficacy of butyrate fermented in aloe vera juice to autism spectrum disorder**

A 40 year-old man who was found out autism spectrum disorder at 3-year-age by the support center for autistic and developmental disorder, was diagnosed as an attention-deficit/hyperactivity and learning disorder, and administered an anticonvulsant, carbamazepine. His medical history showed that his mother had a hard delivery and 36-hour-duration of labor and pregnancy toxemia. On January 2013 at 30-year old, he entered into autism facility after his mother died. He fell unconscious several times and showed severe bad blood examination results. Then, he was prescribed carbamazepine 200mg-400mg/day with gastrointestinal drug and laxatives. He started to ingest aloe vera juice (AVJ) 250ml/day with carbamazepine from February 2013. Since then he provided remission for normal blood examination results, no constipation and no faint attack. Carbamazepine with adjunctive use of AVJ suggested improvement of gut intestinal ecology in ASD patient. Constipation was only gastrointestinal disorder in ASD children and was alleviated with ingestion of AVJ<sup>[17]</sup>.

**Case report 2; Suppression and transition of childhood epilepsy with the medicine and AVJ ingestion as an adjuvant**

A 4-years male child diagnosed epilepsy on April, 2020 and administered anti-psychologic medicine, risperdal 1mg/day for one year. But he did not recover well and stopped administration the drug and changed to ingest AVJ 100ml/day in 5-years old. Since then he did not have any convulsive seizure for one year to April, 2022. He has a well-being QOL on June, 2022.

**Case report 3: Suppression of childhood epilepsy with the medicine and AVJ ingestion as an adjuvant**

A 3-years old male child showed developmental disorders, a likely epilepsy syndrome and at 5-years old he diagnosed epilepsy on April, 2020 and administered aripiprazole 1mg/day. On March, 2022 he stopped administration of the drug, because of the side effect of aripiprazole and started to ingest with AVJ 100ml/day on April, 2022. Since then he controls the seizures of epilepsy and has a well-being QOL on June, 2022.

## DISCUSSION OF CASE REPORTS

Chronic kidney disease (CKD) is a global health problem that brings to a substantial risk for end-stage renal disease. In CKD the accumulation of gut-microbiota derived uremic toxins, such as p-cresol sulfate and etc., accelerates the progression of CKD and mortality<sup>[21]</sup>. In ASD an oral gastrointestinal-restricted adsorbent AB2004 has affinity for small phenolic molecule p-ethylphenol sulfate, p-cresol glycoside and etc. In CKD and ASD it was demonstrated that the disease providing uremic toxins and relieving the anxiety-like behaviors was driven by a gut microbial metabolite with small phenolic molecules. Temporal lobe epilepsy (TLE) is the most common type of pharmaco-resistant epilepsy, which easily gets out of control in human adults. Fujita *et al*<sup>[22]</sup> profiled urinary volatile organic compounds (VOCs) in a mouse model of TLE using solid-phase micro-extraction by gas-chromatography-mass-spectrometry. Thirteen urinary VOCs exhibited differential abundance between epileptic and control mice, and the corresponding areas under the receiver operating characteristic curve were greater than 0.8. Stepwise linear discriminant analysis extracted methanethiol, disulfide, dimethyl, and 2-butanone as predictors. The results suggested that TLE induced by amygdala stimulation could affect both endogenous and metabolites and the gut flora.

In case report 1 a 49-years old man who was found out ASD at 3-years-age administered carbamazepine, the efficacy

of carbamazepine with AVJ as an adjuvant was demonstrated, suggesting the improvement of gut intestinal ecology in ASD patient with AVJ ingestion as an adjuvant. In case report 2 and 3 the drug administration and AVJ ingestion were shown in epilepsy children. The drug administration in the developmental stage of childhood may bring in hazardous of the disorder. In the situation it is strongly important to arrange the intestinal ecosystem and harmonize the children mind with the development of body, suggesting that the establishment of intestinal ecosystem in childhood is not due to the drug-efficacy, but the diet with AVJ-ingestion and a love toward the child in the every-day life. The role of the microbiome and the gut-brain axis in epilepsy cannot be ignored.

## SUMMARY

Possible prophylaxes of histone deacetylase inhibitor butyrate fermented in Aloe vera gel were discussed on the brain histone acetylation and reduction of phenolic metabolites in ASD-patient and epilepsy children. The drug and epigenetic butyrate fermented in AVJ ingestion as an adjuvant may improve symptoms associated with ASD in case 1 report. Case report 2 and 3 strongly suggested the importance of balance between the intestinal microbiota and the developmental body in childhood on the medicinal care of epilepsy. Diet quality should be improved to children with epilepsy.

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