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Case Report

Efficacy of Aloe Fermented Butyrate to Autism Spectrum Disorders

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Abstract

Butyrate is a metabolite of short chain fatty acid by the gut microbiota in large intestine. Butyrate is main energy source for enterocyte regeneration and modulates the enteric microbial community and contributes to impact on intestinal health and host well-being with its beneficial activity in inflammation and neurological disorders. The gut microbiome has played a crucial role in the multi-directional gut-brain axis that integrates the gut and central nerve system activities, and thus a concept of microbiome-gut-brain axis is emerging. In this review, we describe the putative efficacy of gut butyrate to autism spectrum disorders (ASD) and exhibit a case report of ASD patient with aloe vera juice adjuvant.

Keywords: *Immune Modulation; Endophytically Fermented Aloe Butyrate; Microbiome-Gut-Brain Axis; Autism Spectrum Disorders; A Case Report*

Introduction

For a long time, the bacterially derived short chain fatty acids (SCFAs) were believed to be absorbed in colon predominantly via non-ionic diffusion. Sivaprakasam., *et al.* [1] clearly reported that the process is primarily carrier-mediated. Transporters for SCFA have been identified and are expressed both in the lumen-facing apical membrane and the serosa-facing basolateral membrane of colonic epithelial cells. The ATP-dependent efflux transporter ABCG2 (ATP binding cassette transporter, gene family G, member 2), which accepts butyrate as a substrate, is expressed in the apical membrane; it mediates the efflux of butyrate from the cells, but little is unknown on the relative contribution of this transporter to the overall handling of butyrate by the colonic epithelium. SCFA, particularly butyrate, serves as a major metabolic fuel for colonic epithelium; therefore, the transporters responsible for the entry of SCFA are critical for colonic health. The SCFA butyric and propionic acid are often reduced in a dysbiotic state, causing an inflammatory environment and affecting the central nervous system. The influence by allowing hosts to adapt to changes in their intestinal gut surroundings offers important insight into how changes in our gut affect distant organ like our brain. Autism spectrum disorder (ASD) manifests as alterations in complex human behaviors including social communication and stereotypies. In addition to genetic risks, the gut microbiome differs between typically developing and ASD individuals, though it remains unclear whether the microbiome contribute to symptoms. We describe putative efficacy of butyrate to ASD patients and aloe vera juice adjuvant in case report.

Correlation of autism spectrum disorders with gut microbiota

The knowledge gained in recent years about the function and importance of the microbiome has broadened the concept of the gut-brain-axis to the "microbiota-gut-brain-axis", emphasizing the importance of the microbiome in the regulation of gut-brain communica-

tion. The microbiota has the potential to affect neuronal function directly or indirectly through vitamins, neurotransmitters and SCFAs. Autism spectrum disorders (ASD) are complex neurobiological disorders that impair social interactions and communication and lead to restricted, repetitive, and stereotyped patterns of behavior, interests, and activities.

Microbiota transfer therapy altering gut ecosystem and improving gastrointestinal and autism symptoms in children

Kang., *et al.* [2] demonstrated a small open-labeled clinical trial evaluated with the impact of microbiota transfer therapy (MTT) on gut microbiota composition and gut intestinal (GI) and ASD symptoms of 18 ASD-diagnosed children. The gastrointestinal Symptom Rating Scale revealed an approximately 80% reduction of GI symptoms at the end of treatment, including significant improvements in symptoms of constipation, diarrhea, indigestion, and abdominal pain. Improvements persisted 8 weeks after treatment. Clinical assessments showed that behavioral ASD symptoms improved significantly and remained improved 8 weeks after treatment ended. Bacterial and phage-deep sequencing analyses revealed successful partial engraftment of donor microbiota and beneficial changes in the gut environment. Specially, overall bacterial diversity and the abundance of *Bifidobacterium, Prevotella* and *Desulfovibrio* among other taxa increased following MTT and these changes persisted after treatment stopped.

Long-term benefit of microbiota transfer therapy on autism spectrum disorders and gut microbiota

Kang., *et al.* [3] previously performed an open-label trial of microbiota transfer therapy (MTT) that combined antibiotic, a bowel cleanse, a stomach-acid suppression, and fecal microbiota transplant and observed significant improvements in gastrointestinal (GI) symptoms, autism-related symptoms, and gut microbiota. The authors reported on a follow-up with the same 18 participants two years after treatment was completed. Notably, most improvements in GI symptoms were maintained and autism-related symptoms improved even more after the end of treatment. Important changes in gut microbiota at the end of treatment remained at follow-up, including significant increase in bacterial diversity and relative abundances of *Bifidobacteria* and *Prevotella*. The authors demonstrated the long-term safety and efficacy of MTT as a potential therapy to treat children with autism spectrum disorders (ASD) who have GI problems. Furthermore, Kang., *et al.* [4] aimed to detect fecal metabolites that may be present at significantly different concentrations between 21 children with ASD and 23 neuro-typical children and to investigate its possible link to human gut microbiome. Of the 59 metabolites detected, isopropanol concentrations were significantly higher in feces of children with ASD after multiple testing corrections. Fisher Discriminant Analysis with leave-out-validation suggested that a group of metabolites: caprate, nicotinate, glutamine, thymine, and aspartate, may potentially function as a modest biomarker to separate ASD participants from the neuro-typical group. On consistent with Arizona cohort study, the authors confirmed lower gut microbial diversity and reduced relative abundances of phylotypes most closely related to *Prevotella copri* in children with ASD. Xu., *et al.* [5] summarize published data and analyzed the alteration of the relative abundance of bacterial genera in the gut microbiota in controls and individuals with ASD using meta-analysis. The meta-analysis suggests an association between ASD and alteration of microbiota composition.

Gastrointestinal flora and gastrointestinal status in children with autism

Gastrointestinal flora and gastrointestinal status were assessed by Adams., *et al.* [6] from stool samples of 58 children with autism spectrum disorders (ASD) and 39 healthy typical children of similar ages. Children with autism had much lower levels of total SCFAs including lower levels of acetate, propionate and valerate; this difference was greater in the children with autism taking probiotics, but also significant in those not taking probiotics. Children with autism had lower levels of species of *Bifidobacteria* and higher levels of species of *Lactobacillus*, but similar levels of other bacteria and yeast using standard culture growth-based techniques. Lysozyme was somewhat lower in children with autism, possibly associated with probiotics usage. Other markers of digestive function were similar in both groups. The low level of SCFAs was partly associated with increased probiotic use, and probably partly due to either lower production (less saccharolytic fermentation by beneficial bacteria and/or intake of soluble fiber) and/or greater adsorption into the body (due to longer transit time and/or increased gut permeability). Coretii., *et al.* [7] investigated the gut microbiota (GM) structure and fecal SCFAs levels in a cohort of young children (2 - 4 years of age) with ASD, with respect to age-matched neurotypical healthy controls. Strong increase of

Bacteroidetes and *Proteobacteria* and decrease of *Actinobacteria* was observed in these patients. Among the 91 OTUs whose relative abundance was altered in ASD patients, the authors observed a striking depletion of *Bifidobacterium longum*, one of the dominant bacteria in infant GM and conversely, an increase of *Faecalibacterium prausnitzii*, a late colonizer of healthy human gut and a major butyrate producer. High levels of *F. prausnitzii* were associated to increase of fecal butyrate levels within normal range, and over representation of Kyoto Encyclopedia of Genomes (KEGG) functions related to butyrate production in ASD patients. The authors reported unbalance of GM structure with a shift in colonization by gut beneficial bacterial species in ASD patients as off early children. Sun., *et al.* [8] evaluated the occurrence and clinical characteristics of ASD associated to the stable state of the gut microbiota in children. The abundance of *Bacteroidales* and *Selenomonadales* was significantly lower in the ASD group than in the healthy control (HC) group. The abundance of *Ruminococceae* in the ASD group was higher than in the HC group, while the amount of *Prevotellaceae* was significantly lower in the ASD group than in the HC group. The Tax4F analysis based on KEGG data indicated differentially expressed functional pathway between the ASD group and the HC group associated to the nervous system, environmental information processing and cellular processing. The differences affect the biological function of the host. The results suggest that a disorder in the gut microbiota may be associated, at least in part, with ASD in children.

Potential impacts of melatonin on gut microbiome and mitochondria

Rose., *et al.* [9] compared mitochondrial (Mtc) function in rectal and cecum biopsies under the assumption that certain microbiome metabolites, such as butyric and propionic acid, are more abundant in the cecum as compared to the rectum. Rectal and cecum mucosal biopsies were collected during elective diagnostic colonoscopy. Using a single-blind case-control design, complex I and IV and citrate synthase activities and complex I-V protein quality from 10 children with ASD, 10 children with Crohn's disease and 10 neurotypical children with nonspecific GI complaints were measured. Mtc function in the gut mucosa from children with ASD was found to be significantly different than other groups who manifested similar GI symptomatology. Abnormalities localized to the cecum suggest a role for imbalances in the microbiome, potentially in the production of butyrate, in children with ASD. Rose., *et al.* [10] have developed a lymphoblastoid cell line (LCL) model of ASD, with a subset of LCLs demonstrating mitochondrial (Mtc) dysfunction (AD-A) and another subset of LCLs demonstrating normal Mtc function (AD-N). Given the positive modulation of butyrate on Mtc function, the authors hypothesized that butyrate would have a preferential positive effect on AD-A LCLs. To this end, the authors measured Mtc function in ASD and age-matched control LCLs, all derived from boys, following 24 and 48h exposure to butyrate (0, 0.1, 0.5 and 1 mM) both with and without an *in vitro* increase in reactive oxygen species. The data show that the enteric microbiome-derived SCFAs, butyrate modulates Mtc activity, with this modulation dependent on concentration, microenvironment redox state, and the underlying Mtc function of the cell. In general, these data suggest that butyrate can enhance Mtc function in the context of physiological stress and/or Mtc dysfunction and may be an important metabolite that can help rescue energy metabolism during disease states. Thus, insight into this metabolic modulator may have wide applications for both health and disease since butyrate has been implicated in a wide variety of conditions including ASD. Anderson [11] reviewed that two impact hubs have emerged as cutting edge areas of research across a diverse array of medical conditions, the gut microbiome and mitochondria (Mtc). The gut microbiome, especially via its production of butyrate can have a significant impact on immune inflammatory processes. Lower levels of butyrate producing bacteria can increase gut permeability, thereby increasing immune inflammatory activity. The induction of melatonin by butyrate may be feedback on the microbiome via melatonin increasing gut bacteria swarming, as well as melatonin optimizing gut barrier and Mtc functioning. Thus, gut dysbiosis has a significant impact on central and systemic homeostasis, via decreased butyrate and melatonin driving suboptimal Mtc functioning. Many of butyrate's effects seem mediated via Mtc, with butyrate enhancing Mtc functioning under oxidative stress. Decreases in the bacterial families producing butyrate seem of particular importance, with butyrate not only maintaining the integrity of the gut barrier, but also crossing the gut barrier where it can dampen immune and glia cell inflammatory process.

A possible link between the gut microbiota and autism spectrum disorders

Srikantha and Mohajeri [12] review focuses on specific alterations of gut microbiota mostly observed in autistic patients. Particularly, the mechanisms through which such alterations may trigger the production of the bacterial metabolites, or leaky gut in autistic people

are described. Various altered metabolite levels were observed in the blood and urine of autistic children, many of which were of bacterial origin such as SCFAs, indoles and lipopolysaccharides. Lower concentrations of the total amount of SCFAs are found in autistic children, providing the evidence for a reduced fermentation capacity of the microbiota. Butyrate is said to be the most important SCFA in humans as it exhibits neuroprotective features. It promotes memory formation and neuronal plasticity through epigenetic modulation. In some neurodegenerative models butyrate was found to ameliorate symptoms. Furthermore, a less integrative gut-blood-barrier is abundant in autistic individuals. This explains the leakage of bacterial metabolites into the patients, triggering new body responses or an altered metabolism. The authors suggested that ASD is associated with an unbalanced gut microbiota. Although the cause-effect relationship between ASD and gut microbiota is not yet well established, the consumption of specific probiotics may represent a side-effect free tool to re-establish gut homeostasis and promote gut health. The authors presented several epidemiologic, experimental human and *in vivo* studies for the involvement of different microbes in the ASD pathology, such as *Clostridia* spp. highlighted the evidence for several metabolites to be considered as possible biomarkers for ASD.

Mohajeri., *et al.* [13] review on relationship between the gut microbiome and brain function. Butyrate is said to be the most important SCFA in humans as it exhibits neuroprotective features. It promotes memory formation and neuronal plasticity through epigenetic modulation. Even if not conclusive, the data suggest an involvement of increased acetate and propionate and decreased butyrate in the pathophysiology of ASD.

Health benefits of aloe fermented butyrate to autism

Multiple beneficial effects of butyrate fermented in aloe vera gel on intestinal and extra-intestinal level had been demonstrated [14-16]. The mechanisms of action of butyrate are different and many of these involve an epigenetic regulation of gene expression through the inhibition of histone deacetylase. The impact on epigenetic alterations should lead to more specific and efficacious therapeutic strategies for the prevention and treatment of various diseases, ranging from genetic metabolic conditions to neurological degenerative disorders.

Cohort study of autism spectrum disorder in early childhood

Leptin is a hormone produced directly from adipocyte and has been associated with type2 DM which is characterized by insulin resistance. Leptin is a pro-inflammatory cytokine that plays an important role in energy homeostasis. Energy evidence suggests that leptin levels are altered in children with autism spectrum disorder (ASD); however, this has not been studied prospectively. Are early life growth and a biomarker leptin related to ASD risk? To answer this question, Raghavan., *et al.* [17] followed 822 children from birth and found that those who gained weight very quickly in infancy, had higher leptin levels in early childhood, had a greater chance of later ASD-diagnosis.

Altered gut microbiota and short chain fatty acids in autism spectrum disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by impairments in social interactions and communication, restricted interests and repetitive behaviors. Liu., *et al.* [18] sequenced the bacterial 16SrRNA gene, detected fecal SCFAs, assessed gastrointestinal (GI) symptoms and analyzed the relationship between the gut microbiome and fecal SCFAs in autistic and neuro-typical individuals. The results showed that the compositions of the gut microbiota and SCFAs were altered in ASD individuals. The authors found lower levels of fecal acetic acid and butyric acid and a higher level of fecal valeric acid in ASD subjects. The authors identified decreased abundances of key butyrate-producing taxa and an increased abundance of valeric acid associated bacteria among autistic individuals. Constipation was the only GI disorder in ASD children. It is suggested that the gut microbiota contributes to fecal SCFAs and constipation in autism. Modulating the gut microbiota, especially butyrate-producing bacteria, could be a promising strategy in the search for alternatives for the treatment of autism spectrum disorders.

Association of maternal type 1 diabetes with autism in offspring

The association of maternal diabetes and autism spectrum disorders (ASDs) in offspring was investigated by Xiang., *et al* [19]. The authors assessed ASD risk associated with intrauterine exposure to preexisting type2 diabetes and gestational diabetes mellitus (GDM)

by gestational age at GDM diagnosis. Retrospective longitudinal cohort study including 322,323 singleton children born in 1995 - 2009 at KPSC hospitals was designed. In this large, multiethnic clinical cohort of singleton children born at 28 to 44 weeks' gestation, exposure to maternal GDM diagnosed by 26 weeks' gestation was associated with risk of ASD in offspring. The authors [20] extended previous observations by examining the risk of ASD in offspring associated with maternal T1D, T2D, and GDM. Of 419,425 children (boys, 51%) meeting study criteria, 631 were exposed to maternal T1D, 9,453 to maternal T2D, 11,922 to GDM diagnosed after 26 weeks' gestation, and 24,595 to GDM diagnosed after 26 weeks' gestation. During a median follow-up of 6.9 year, 5,827 children were diagnosed with ASD. Unadjusted average annual ASD incidence rates per 1,000 children were 4.4 for exposure to T1D; 3.6 for T2D; 2.9 for GDM by 26 weeks; 2.1 for GDM after 26 weeks; and 1.8 for no diabetes. Furthermore, Xiang., *et al.* [21] showed that maternal preexisting type1, type2, or gestational diabetes diagnosed relative early in pregnancy are associated with increased risk for ASD in offspring. This study extends previous observation by examining the association between maternal hemoglobin A1C level during pregnancy and risk of ASD in offspring.

Maternal diabetes and hypersensitive disorders in association with autism spectrum disorders

Cordero., *et al.* [22] studied if common complications in pregnancy are associated with ASD in a large sample of mothers and children. Children were classified into three groups based on confirmation of ASD (n = 698), non-ASD development delay (DD; n = 887), or controls drawn from the general population (POP; n = 979). Among 2,564 mothers, the authors identified 246 (9.65%) with any diabetes and 386 (15.1%) with any hypertension in pregnancy. After adjustment for covariates, any diabetes during pregnancy was not associated with ASD, but any hypertension was associated with ASD. Results were similar for DD and any diabetes or any hypertension. The results showed an association between conditions marked by high blood pressure and ASD, but no association with conditions marked by high blood sugar and ASD. Associations were similar for children who had a developmental disorder that was not ASD, suggesting that this relationship may not be specific to ASD. Furthermore, Windham., *et al.* [23] examined both in the study to explore early development, a multi-site case-control study of children born in 2003 - 2006. Children identified from clinics, schools and birth certificates were enrolled at ages 2 - 5 year and using standardized developmental evaluations, classified as: ASD, other developmental delays, or population-based controls. In a large, national study, the authors found that children with autism were more likely than unaffected children to have mothers with higher weight gain during pregnancy; risk of autism may be even stronger if mothers were also overweight before pregnancy. Children with other developmental delays were more likely to have mothers who were overweight or obese before pregnancy, but not who gained more weight during pregnancy. Overweight and weight gain may represent factors that could be modified.

A prebiotic intervention study in children with autism spectrum disorders

Different dietary approaches, such as gluten and casein free diets, or the use probiotics and prebiotics have been suggested in autism spectrum disorders (ASD) in order to reduce gastrointestinal (GI) disturbances. Grimaldi., *et al.* [24] assessed the impact of exclusion diets and a 6-week Bimuno galacto-oligosaccharide (B-GOS) prebiotic intervention in 30 autistic children. The results showed that children on exclusion diets reported significantly lower scores of abdominal pain and bowel movement, as well as lower abundance of *Bifidobacterium* spp. and *Veillonellaceae* family, but higher presence of *Faecalibacterum prausnitzii* and *Bacteroides* spp. Following B-GOS intervention, the authors observed improvement in anti-social behavior, significant increase of *Lachnospiraceae* family and significant changes in fecal and urine metabolites. A combined dietary approach of a prebiotic and exclusion diets resulted in a significant improvement in antisocial behavior suggesting that such approaches might be more relevant for improvement of these aspects as well as psychological traits.

Sharon., *et al.* [25] transplanted gut microbiota from human donors with ASD or typically developing controls into germ-free mice and revealed that colonization with ASD microbiota is sufficient to induce hallmark autistic behaviors. The authors proposed that the gut microbiota regulates behaviors in mice via production of neuroactive metabolites, suggesting that gut-brain connections contribute to the pathophysiology of ASD. Repetitive and social behavioral abnormalities in mice with microbiomes from patients with ASD can be corrected by the administration of specific metabolites.

Butyrate profiling and higher level of macrophage migration inhibitory factor in autism spectrum disorders

Butyrate is said to be the most important SCFA in humans as it exhibits neuroprotective features. It promotes memory formation and neuronal plasticity through epigenetic modulation. Mohajeri., *et al.* [13] exhibited that butyrate was found to ameliorate symptoms in some neurodegenerative models. Even if not conclusive, the data suggest an involvement of increased acetate, and propionate and decreased butyrate in the pathophysiology of ASD.

Intestinal phagocytes and tissue-resistant macrophages in particular, act as an innate barrier in the intestine by clearing invading bacteria. Malfunctioning of this pathway is involved in the pathogenesis of inflammatory bowel disease (IBD) since defective microbicidal responses were identified in polygenic and monogenic forms of IBD. Macrophage migration inhibitory factor (MIF) is a pivotal regulator on innate immunity and inflammatory and was higher in autism than in normal developmental children. Ning., *et al.* [26] investigated the influence of serum levels of MIF on ASD severity on one hundred and two Chinese children with ASD who were significantly higher than those of control subjects, and exhibited that MIF improved the combined model such as HCY/CRP/IL-6, to predict severe ASD.

Butyrate boosts microbicidal macrophages

Microglia is tissue macrophage cells located in the brain that participate in immune responses including removal of dead cells and pathogens. As the tissue macrophages of the CNS, microglia is critically involved in diseases of the CNS. Erny., *et al.* [27] observed substantial contributions of the host microbiota to microglia homeostasis, as germ-free mice displayed global defects in microglia with altered cell proportions and an immature phenotype, leading to impaired innate immune responses. The findings suggest that host bacteria vitally regulate microglia maturation and function, whereas microglia impairment can be rectified to some extent by complex microbiota.

Schulthess., *et al.* [28] have shown that macrophages differentiated in the presence of the bacterial metabolite butyrate display enhanced antimicrobial activity. Butyrate-induced antimicrobial activity was associated with a shift in macrophage metabolism, a reduction of mTOR kinase activity, increased LC3-associated host defense and anti-microbial peptide production in the absence of an increased inflammatory cytokine response. Butyrate drove this monocyte to macrophage differentiation program through HDAC3 inhibition. The data suggest that (1) increased intestinal butyrate might represent a strategy to bolster host defense without tissue damaging inflammation and (2) that pharmacological HDAC3 inhibition might drive selective macrophage functions toward antimicrobial host defense. Butyrate inhibits HDAC3 to drive metabolic changes and microbicidal function.

Case Report

Adjunctive use of aloe vera juice to autism spectrum disorder patient

A 40-year-old man who was found out ASD at 3-year-age by Support center for autistic disorder and developmental disorder, was diagnosed as an attention-deficit/hyperactivity and learning disorder and administered 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 sever bad blood examination results. Then, he was prescribed carbamazepine 200 - 400 mg/day with gastrointestinal drug and laxatives. He started to ingest aloe vera juice (AVJ) 250 ml/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 is suggested improvement of gut intestinal ecology in ASD patient. Constipation was only gastrointestinal disorder in ASD children and was alleviated with ingestion of AVJ. Possible prophylaxes of AVJ with L-arginine and CQ10 as adjuvant to enhance chronic fatigue syndrome and muscle performance respectively were reported in earlier papers [29,30]. The case report demonstrated carbamazepine with adjuvant AVJ supports a good quality of life to ASD patient.

Summary

ASD are characterized by disconnectedly due to disordered neuronal migration and by neuronal mitochondrial dysfunction. Different pathways involved in neuronal migration are affected by intrauterine hyperglycemia and hyperinsulinemia, while prolonged neonatal hypoglycemia may cause mitochondrial dysfunction.

The PubMed searching by Hoirisch-Clapauch., *et al.* [31] with the Medical subject headings (MeSH) terms "autism spectrum disorder (ASD)" and "risk factor" demonstrated that of 158 neonates selected to be screened according to maternal life style risk factors, 48 had hypoglycemia. Glucose abnormalities in the embryo, the fetus or the neonate, seem to have a role in the pathogenesis of ASD. Controlled studies are needed to clarify whether interventions aimed at maintaining glycemic control throughout pregnancy, together with new screening programs for neonatal hypoglycemia are effective in reducing the prevalence of ASD.

ASD symptoms were reduced nearly 50% two years after fecal transplant therapy, suggesting a link between gut microbiome in individuals with ASD. Modifying the gut microbiome is a potential route to improve gastrointestinal and behavioral symptoms in children with ASD. Fecal microbiota transplantation could transform the dysbiotic gut microbiome toward a healthy one by delivering a large number of commensal microbes from a healthy donor.

The gut microbiota and its metabolites, especially short chain fatty acids (SCFAs), butyrate, play an important role in gastrointestinal disorders, and contribute to fecal SCFAs and constipation in autistic subjects. Disturbance of the microbiome-gut-brain axis may be associated with the pathogenesis of ASD.

In addition, a case report on ASD patient suggests that aloe vera adjuvant with carbamazepine supports improvement of gut intestinal ecology and QOL in ASD patient.

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