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REVIEW ARTICLE

ALSUntangled #64: butyrates

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Abstract

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). Here we review butyrate and its different chemical forms (butyrates). Butyrates have plausible mechanisms for slowing ALS progression and positive pre-clinical studies. One trial suggests that sodium phenylbutyrate (NaPB) in combination with Tauroursodeoxycholic acid (TUDCA) can slow ALS progression and prolong survival, but the specific contribution of NaPB toward this effect is unclear. Butyrates appear reasonably safe for use in humans. Based on the above information, we support a trial of a butyrate in PALS, but we cannot yet recommend one as a treatment.

Keywords: *ALS, butyrate, gut microbiome, neuroinflammation, alternative therapy*

ALSUntangled reviews alternative and off-label treatments on behalf of people with amyotrophic lateral sclerosis (PALS). Here we review the use of butyrates, for which we have had 150 requests (1).

Overview

Butyrate is a short-chain fatty acid, naturally produced through fermentation of undigested fiber by the gut microbiome. Within the gut, it can influence epithelium integrity, inflammation, and the risk of gastrointestinal disorders (2–5). Butyrate is sometimes administered as treatment for inflammatory bowel disease (5). There is growing evidence that butyrate and its metabolites can leave the gut and influence neurological diseases via a "gut brain axis (6–9)." At least one website suggests that butyrate is a "promising" treatment for ALS (10).

Butyrate itself is difficult to study as an oral supplement due to its unpleasant "sour-milk" odor, and its rapid absorption by cells in the upper GI tract with limited penetration into the bloodstream (11). Methods for overcoming these

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Table 1. Table of evidence for Butyrate.

	Grade	Explanation
Mechanism	A	One form of butyrate (NaPB) can alter histone acetylation in PALS and other forms can reduce inflammation and improve energy metabolism at least in cell and animal models
Pre-Clinical	A	Well-designed, independently replicated studies in an ALS mouse model suggests that butyrates can improve gut integrity, delay disease onset and improve survival
Cases	C	One PALS with a validated diagnosis experienced recovery of lost motor function on NaPB (along with several other treatments)
Trials	U	We found 2 trials of NaPB in PALS. One showed no clinical benefit but was underpowered. The other (using a combination of NaPB and TUDCA) showed benefits in ALSFRS-R progression and survival, but the exact contribution of NaPB to the effects cannot be determined
Risks	C	More than 10% of PALS experienced non-serious adverse events in a previous open label trial

problems include colonic delivery of butyrate via enema (11), use of microencapsulated formulations (11), or use of formulations (butyrates) in which butyrate is conjugated with cations, such as sodium butyrate (NaB, 12), or conjugated to other molecules, such as sodium phenylbutyrate (NaPB, 13). NaPB is a prescribed medication used to reduce ammonia in some subtypes of urea cycle disorders and short-chain fatty acid disorders. Butyrate can cross the blood brain barrier (9).

Mechanisms

Butyrates have at least 3 mechanisms by which they could affect the progression of ALS: altering transcription, reducing neuroinflammation, and improving cellular energy metabolism.

Altering transcription

Alterations in histone acetylation leading to transcriptional dysregulation (abnormal patterns of genes that are turned on) occur in PALS and are believed to contribute to disease progression (14). Butyrates can enter cells and act as histone deacetylase inhibitors (15–17). One human study showed that oral NaPB can restore a more normal pattern of histone acetylation in the blood of PALS (14).

Reducing neuroinflammation

Inflammation is believed to be involved in ALS progression and is a common therapeutic target in ALS trials (18). Butyrate reduces colonic inflammation by modulating the function of T-cells (17,19). It can also alter peripheral inflammation in animal models. This includes promoting expansion of regulatory T cells in vitro (20), a specialized type of immune system modulating cell known to be reduced in PALS (21) and reducing circulating pro-inflammatory cytokines (22). Relevant to the brain, NaB can attenuate microglial-induced inflammation, at least in cell cultures (23–25).

Improving energy metabolism

Recent reviews highlight energy metabolism alterations in PALS (26,27), which are also being targeted in clinical trials. Butyrate itself can be used by cells as an energy source, and it appears capable of upregulating genes involved in mitochondrial synthesis and function in cell and animal models (8,9,28).

While all these mechanisms have been demonstrated in cell and animal models, the finding that NaPB can affect histone acetylation in PALS means that ALSUntangled assigns a TOE "Mechanism" grade of A (Table 1).

Pre-clinical models

Within the G93A mSOD1 mouse model of ALS, abnormally increased gut permeability and reduced numbers of butyrate-producing bacteria appear before neurological deficits are apparent (29). Three published studies in this mouse model show that NaB or NaPB treatment can delay the onset of motor deficits, prolong survival, and improve motor function. In one study, butyrate-treated mSOD1 mice were started on NaB at age 63 days, and disease onset was prolonged by 40 days (age of 150 days versus 110 days). This group had a prolonged life span of 38 days (178 versus 140 days) (30). In another study that assess for NaPB, intraperitoneal administration of NaPB at 200 and 400 mg/kg/day significantly extended survival by 8.6 and 21.9% respectively, compared with untreated mice (137 and 153 days versus 126 days in the control group) (31). In addition to disease onset and life span, motor function was also assessed in different studies by the rotarod performance test where mice were placed onto the rotating rod, and latency to fall was recorded when the mouse fell from the rod. Mice treated with NaB or NaPB had a significantly longer latency to fall in the rotarod test (31,32). These studies are generally well designed, and the results are replicated across two separate groups of investigators. Based on these studies, ALSUntangled assigns a TOE "Pre-Clinical Models" grade of A (Table 1).

Data in PALS

Cases

In the online community PatientsLikeMe, 4 members report taking NaPB, 2 report taking NaB, 1 reports taking calcium magnesium butyrate, 1 reports taking butyrin, and 1 reports taking butyric plex as a treatment for ALS. Of these, only 2 (on NaPB) completed treatment evaluations (33); one rated effectiveness as "moderate" and the other "can't tell." Within the cohort of "ALS Reversals" being studied at Duke University (34,35), one was taking NaPB (along with several other treatments) during their recovery. Based upon this case with validated diagnosis and recovery associated with NaPB, we assign a TOE "Cases" grade of C (Table 1). As we have mentioned previously, an association between a treatment and an ALS Reversal does not mean one caused the other; there are many possible explanations for ALS Reversals (35).

Trials

We found 2 trials of butyrates in PALS. The first was an open label trial of 40 PALS treated with escalating doses of NaPB (9–21 grams per day) for 20 weeks (14). Fourteen patients dropped out of the study early, 7 for adverse events possibly related to treatment. Histone acetylation of blood cells changed with NaPB treatment, but no improvement in clinical measures of disease progression (ALSFRS-R, FVC or grip strength) was detected compared to historical controls. This study was underpowered to detect changes in such measures. The second trial sponsored by Amylyx was randomized, double-blind and placebo-controlled phase 2 study (36,37). Eighty-nine PALS received a combination of NaPB (3grams twice a day) and Tauroursodeoxycholic acid (TUDCA) (1gram twice a day) called AMX0035 and 48 PALS received a placebo. After 24 weeks in the blinded portion of the trial, participants could enter an open label extension. Sixty-nine percent of PALS receiving NaPB and 77% of PALS receiving placebo completed the blinded portion of the trial. Disease progression, as measured by ALSFRS-R (36) and survival (37) was significantly better in the NaPB-treated patients compared to the placebo-treated patients. A randomized, double-blind, placebo-controlled, multicenter phase III trial sponsored by Amylyx is currently recruiting patients. This trial aims to evaluate the safety and efficacy of AMX0035 versus placebo for a 48-week treatment (https://clinicaltrials.gov/ct2/show/NCT05021536?term=amx0035&cond=ALS&draw=2&rank=4). Approximately 600 participants with definite or clinically probable ALS within 24 months of symptom onset will be enrolled across more than 70 sites across the U.S. and Europe. Placebo or AMX0035 will be administered for 48 weeks. Primary outcome measures include ALSFRS-R over treatment duration, adverse events, and the number of participants in each group able to remain on the study drug until planned discontinuation. Participants who complete the 48-week trial will have the option to receive AMX0035 after the trial if permitted by each regions' regulatory guidance.

Since TUDCA alone may improve ALS progression (38), it is not possible to delineate the specific contribution of NaPB to the outcomes seen in this trial. Thus, because one trial was underpowered and the other studied NaPB in combination with TUDCA, ALSUntangled assigns a TOE "Trials" grade of U (Table 1).

Of additional interest, some studies suggest a difference in butyrate-producing taxa in the gut microbiome of PALS compared to healthy controls. In a study, DNA extracted from stool samples of six PALS and five healthy controls showed a significant decrease in butyrate-producing taxa, including *Anaerostipes* and *Lachnospiraceae*, in the gut microbiome of PALS (39). In another study, DNA extracted from stool samples of 66 PALS and 61 healthy controls demonstrated that relative abundance of the dominant butyrate-producing bacteria *Eubacterium rectale* and *Roseburia intestinalis* was significantly lower in PALS, as was the total abundance of 8 dominant species capable of producing butyrate (40). In a third study, the gut microbiome of ten PALS and their spouses were explored based on DNA extracted from rectal swabs. Although a deficiency in butyrate-producing microbes was not observed, predictive analysis of microbial enzymes revealed that PALS patients had decreased activity in several metabolic pathways, including butyrate metabolism (41).

There are also human studies examining the influence of the microbiome on ALS progression. In a study comparing the microbiome profile of nineteen PALS with different clinical characteristics, although not statistically significant, PALS with slow-progressing disease had a lower microbial diversity and higher fecal butyrate levels than other progression phenotypes, suggesting the possibilities of using microbiome composition as a biomarker for ALS progression (42). In another study of 49 PALS, the composition of the fecal microbiome of PALS was not significantly different from matched healthy controls, but the complexity of the microbiome appeared to have a significant impact on survival times. PALS with increased diversity of the microbiome had a higher risk of being fast progressors. However, neither the amounts of butyrate nor butyrate-producing bacteria were measured in individual subgroups (43).

Because of the complexity of the gut microbiome, and the phenotypic heterogeneity of ALS,

although rapidly evolving, the understanding of the microbiome in PALS is still limited. The clinical implication of the composition of the gut microbiome, or more specifically butyrate-producing taxa in PALS, is unclear. Nonetheless, with the current knowledge that butyrate can affect the progression of ALS through different mechanisms, it is an emerging area that could be targeted to develop new biomarkers or regulate to slow down ALS progression. Large studies are necessary to decipher this issue. Probiotics have not been tested in PALS.

Dosing, risks, and costs

Butyrate is available in a wide range of doses and formulations. The optimal dosage and form of butyrate for ALS treatment have yet to be established. In the small open label trial of NaPB, 9 grams per day changed histone acetylation patterns, and higher doses did not seem more effective at doing this (14). Ninety eight percent of 40 PALS tolerated 9 grams per day, 84% of 37 PALS tolerated 12 grams per day, 76% of 31 PALS tolerated 15 grams per day, 60% of 29 PALS tolerated 18 grams per day, and 57% of 22 PALS tolerated 21 grams per day. No serious adverse events were seen in the PALS in this study. Adverse events were seen at higher frequencies than expected from a historical placebo group including dizziness (22.5% of PALS), diarrhea (20%), peripheral edema (20%), dry mouth (17.5%), nausea (17.5%), rash (17.5%), fatigue (15%), anxiety (12.5%) and abdominal pain (12.5%). Several additional adverse events are mentioned in the NaPB package insert, but these occurred in children with urea cycle disorders or patients with cancer diagnoses; consequently, it is not clear how applicable they are to PALS (44). With regard to butyrate itself, no adverse reactions or side effects were observed in clinical trials for Crohn's disease with oral administration of 4000 mg per day (45). Based on the open label NaPB trial in PALS (14), ALSUntangled assigns a TOE "Risks" grade of C (Table 1).

It is important to note that there may be marked differences in efficacy and side effect profiles associated with different butyrates. As we have pointed out in reviews of other products, there may even be differences in the formulation of one specific butyrate (ex. NaPB) between different brands/manufacturers. Purchasing a butyrate supplement via a website or even purchasing prescription NaPB through a pharmacy, does not mean the risks and benefits experienced will be similar to those seen in the NaPB and AMX0035 trials described above.

The cost of butyrate will depend on the formulation and dosage selected. NaB (available without a prescription) at 2 grams per day can cost as little as $30 per month (46). NaPB (available by prescription) at a dose of 6 grams per day can cost as much as $4000 per month (47). Insurance generally does not cover the cost of this.

Conclusion

Butyrates have plausible mechanisms for treating ALS and positive preclinical studies replicated by different groups. One PALS appeared to recover lost motor function on NaPB in conjunction with several other treatments; associations such as this do not prove causality. There are 2 trials in which PALS were treated with NaPB. One was underpowered to detect a clinical effect, and the other used NaPB along with TUDCA, so it is impossible to isolate the benefits of NaPB alone. To date, NaB has not been tested in clinical trials in PALS. Butyrates can have common side effects, and some forms are very expensive. We support further investigation and trials of butyrates in PALS, but we cannot yet recommend any of them as a treatment.

Declaration of interest

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