Strategies for therapeutic restoration of diminished butyrate levels in Machado-Joseph disease

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**ABSTRACT:**

Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), is the most prevalent dominantly inherited form of spinocerebellar ataxia worldwide with no cure. MJD is characterized by progressive loss of movement, speech difficulties, muscle rigidity, abnormal eye movements, and ultimately, wheelchair dependence and death. It is caused by the inheritance of an *ATXN3* gene with overexpanded trinucleotide (CAG) repeats, translating into a long chain of glutamine residues (polyQ tract) within the ataxin-3 protein. Normally, ataxin-3 functions as a deubiquitinating enzyme essential for degrading defective proteins, but the mutant form has a propensity to misfold, oligomerize, and aggregate. The accumulation of these aggregates exerts chronic pressure on neurons, resulting in neuronal loss and disease progression.

Emerging evidence, including studies from our research team, suggests that treatment with sodium butyrate (a sodium salt of butyrate) may have protective effects in experimental models such as transgenic MJD zebrafish. Butyrate is a natural metabolite produced by the microbial fermentation of undigested carbohydrates in the colon. Its functions include inducing autophagy, inhibiting histone deacetylases, maintaining intestinal barrier integrity, inhibiting pro-inflammatory cytokines, and providing an energy source for colonocytes. However, the presence of altered butyrate levels in transgenic MJD mice compared to wild-type littermates remains elusive. If MJD mice have lower butyrate levels, supplementing them with butyrate could offer a therapeutic approach. While there are established methods to elevate fecal butyrate levels, including prebiotic, probiotic, and prodrug interventions, whether these treatments can translate to increased circulating and brain butyrate levels remains to be elucidated. Moreover, the specific brain regions exhibiting preferential butyrate uptake and accumulation following such interventions warrants more research.

In this study, we first examined the amount of butyrate present within MJD mouse brains and their wild-type littermates using gas chromatography-mass spectrometry. This revealed significantly lower butyrate levels in the brain of MJD mice than their wild-type counterparts. Furthermore, we compared the effects of eight different butyrate-producing treatment candidates on the levels of butyrate in the plasma, feces, and brain tissue of wild type mice. These findings will inform an efficacy study to further investigate whether butyrate can be used as a potential treatment for Machado-Joseph disease.