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Butyrate enhances mitochondria respiration when challenged with oxidative stress

Butyrate is a ubiquitous short-chain fatty acid (4 carbons in length) that has been shown to have many health benefits. Butyrate is principally produced by the trillions of microbial cells that live in our intestine commonly known as the enteric microbiome. These microbes are suspected of affected the health and disease states of our body, both positively and negatively through a variety of biological mechanisms. One of these mechanisms is through the production of short-chain fatty acids like butyrate.

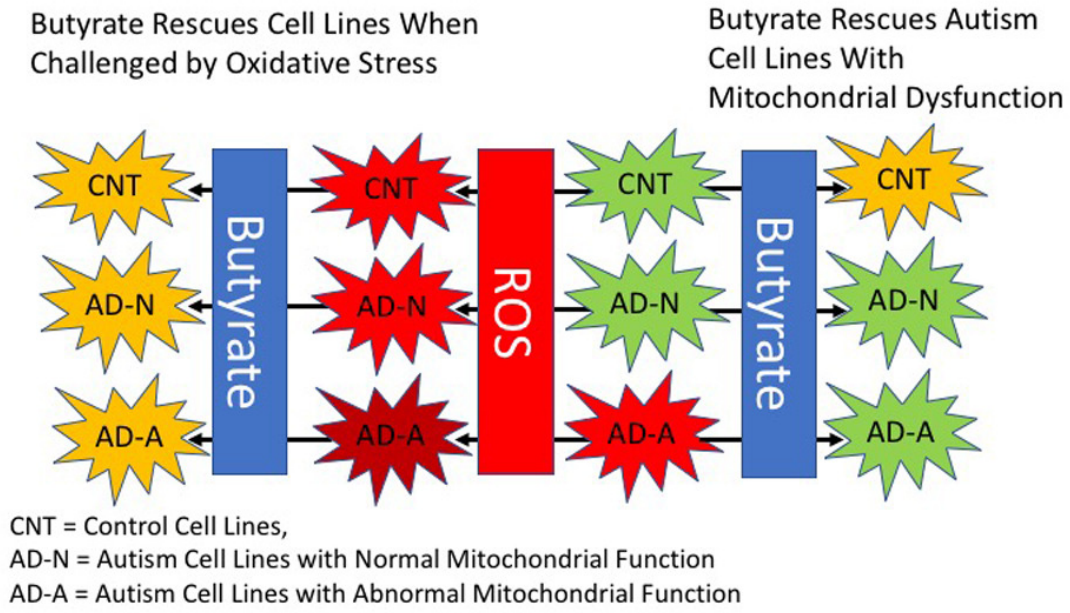

Fig. 1.

Basic research using animal models has suggested that butyrate may be therapeutic in a verity of neurologic and psychiatric conditions including autism spectrum disorder (ASD). One of the potential biological connections between butyrate and ASD is the mitochondria. Butyrate stimulates oxidative phosphorylation and fatty acid oxidation, and, in fact, the mitochondrial of colonocyte (cells that line the inside of the colon) required butyrate to function in germ-free mice. Some individuals with ASD have abnormal mitochondrial function and a majority have high level of oxidative stress which can additionally disrupt mitochondrial function.

A cellular model of mitochondrial dysfunction in ASD we developed was used to better understanding this effect of butyrate on the mitochondria. We developed a lymphoblastoid cell line (LCL) model of ASD, in which a subset demonstrates mitochondrial dysfunction (AD-A) and a subset demonstrating normal mitochondrial function (AD-N) as well as age-matched control (CNT) LCLs. We measured mitochondrial function and gene expression in these LCLs following 24hr or 48hr incubation with different concentrations of butyrate both with and without exposure to reactive oxygen species (ROS).

The findings of our study are outlined in Figure 1. All concentrations of butyrate rescued mitochondrial respiration in ASD LCLs that demonstrated mitochondrial dysfunction at baseline. Some concentrations of butyrate rescued mitochondrial function in the LCLs with normal mitochondrial function at baseline when they were challenged with increased ROS. Linear modeling demonstrated that the effect of butyrate was to better regulate mitochondrial function such that abnormal low mitochondrial function was increased while abnormality high mitochondrial respiration was decreased.

The highest concentrations of butyrate increased expression of genes involved in improving mitochondrial quality, including PINK1, DRP1, FIS1, improving resilience to physiological stress, including UCP2, mTOR, HIF1α, PGC1α, as well as others linked to cognition and behavior, including CREB1, CamKinase II. The findings of our study show that butyrate may enhance the function of abnormally functioning mitochondrial and may protect normally function mitochondria from the negative effects of physiological stress. The highest concentration of butyrate is believed to be similar to concentrations inside the colon while the lowest concentration of butyrate used is closer to blood concentrations once it is absorbed and transported to the liver. However, these concentrations are under normal condition; disorders in which the microbiome bacteria which produce butyrate is disrupted could result in much higher or lower butyrate concentrations. While butyrate could act directly in the brain and body if it is produced at high levels or if it is supplemented in the food, butyrate could also affect the function of the brain and body by affecting the health of the gut and/or influencing gut-associated lymphoid tissue which can modulate the body's immune system.

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Publication

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