Abstract

The Tmem70 protein plays a significant role in the biogenesis of ATP synthase, mutations in the *Tmem70* gene are a common cause of mitochondrial disease and have been associated with neonatal encephalocardiomyopathy. Similar to other mitochondrial disorders, there is currently no available treatment for Tmem70 defects. However, the ketogenic diet (KD) appears to be a potential therapeutic intervention for various mitochondrial disorders, and our preliminary results demonstrate its positive impact in a mouse model of Tmem70 dysfunction. Therefore, using this Tmem70 model, we decided to test a modified KD, which could be a better alternative for a potential application in human patients. The effect of the modified KD was examined in a mouse model of tamoxifen-induced whole-body knockout of *Tmem70* (Tmem70 KO). The modified KD led to improved survival, slowed weight loss, and normalization of plasma indicators of liver damage. We detected a positive effect of the modified KD on the assembly of ATP synthase in liver tissue, however, skeletal muscle showed only a minimal response. Based on the results of this study, we infer that although the absence of functional Tmem70 affects both liver and muscle tissues, the greater impact on the phenotypic manifestation in the Tmem70 KO mouse model is due to liver pathology, which is partially normalized by the modified KD. Our results from the use of the modified KD thus support the hypothesis that the positive effect of both classical and modified KD in Tmem70 defects is caused by ketone bodies themselves rather than the minimization of carbohydrate content in the classical KD. Therefore, modified KD may represent one of the possible approaches for supportive therapy for patients with Tmem70 mutations in the future.

Keywords: mitochondria, ATP synthase, oxidative phosphorylation, Tmem70, mitochondrial diseases, ketogenic diet