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Brain macroautophagy on the ketogenic diet

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Abstract

The ketogenic diet has been shown to be very effective in managing drug-resistant epilepsy, treatment of obesity, improving symptoms of diabetes and reducing cardiovascular risk. Growing evidence supports the use of the ketogenic diet as an alternative or additional therapy in many types of cancer, polycystic ovary syndrome, acne, and neurological diseases. The rationale for the use of the ketogenic diet in brain diseases is based on its neuroprotective properties. But mechanisms responsible for these effects are only partially explained. It is possible that stimulation of macroautophagy (hereafter termed autophagy) may be one of the mediators of the neuroprotection afforded by the ketogenic diet. Autophagy is a key mechanism for maintaining cell homeostasis and therefore its proper function is necessary for preventing accelerated brain aging and neurodegeneration. Autophagy has become a subject of intensive research as a promising target for neuroprotective strategies, which are urgently needed in our aging population, in which the burden of age-related diseases is constantly increasing. The ketogenic diet may induce autophagy in brain cells through at least a couple of mechanisms: downregulation of mTORC1, activation of AMP-activated kinase, elevation of free fatty acids, activation of Sirtuin 1 and an increase of HIF1α expression. The aim of this study was to verify the hypothesis that the ketogenic diet affects the level of autophagy in the mouse brain. Thirty 9-weeks-old male mice were divided into three groups and fed with one of two differently composed ketogenic chows (KA, KB) or with standard rodent chow (SD) for 4 subsequent weeks. Western blotting (LC3, p62) and confocal microscopy (LC3 puncta) were employed to monitor autophagy in hippocampal and cerebrocortical samples. The Western blot results revealed an increased level of LC3 II protein - a marker of autophagosomes, in the hippocampus and frontal cortex of mice treated with ketogenic diet. The size of this effect was dependent on the composition of the diet. This observation was confirmed by the evaluation of the number of LC3 puncta with immunofluorescence microscopy. This study reports for the first time the upregulation of autophagosome synthesis in the brain of animals fed with the ketogenic diet. Our results make a significant contribution to the understanding of the mechanisms of ketogenic diet action. This research is supported by the National Science Center grant no 2017/01/X/NZ3/00984.

Conflict of Interest

There is no conflict of interest