Timed high-fat diet counteracts the disruptive effect of ketogenic diet on circadian brain-derived neurotrophic factor (BDNF) expression and associated signaling

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Ketogenic diet (KD) leads to beneficial metabolic changes and is used to treat epilepsy. In contrast, KD has various side effects and leads to decreased brain-derived neurotrophic factor (BDNF) involved in neuronal development and energy homeostasis centrally and peripherally. Our aim was to test the effect of KD on circadian rhythms and the ability of time-restricted high-fat diet (RF-HFD) to improve the circadian expression of BDNF and associated signaling pathways in mouse brain and liver. Mice were fed KD *ad libitum* and were compared to mice fed high-fat diet *ad libitum* (AL-HFD) or RF-HFD for 2 months. KD led to insulin resistance and increased body weight, food intake and epididymal fat depots levels and these adverse effects could be rectified by timed HF diet. In addition, KD led to a change in the circadian expression of the clock negative feedback loop. *Bdnf* mRNA expression was found to be affected by the increased fat in the diet rather than the timing of food availability. In the brain, KD led to low mature BDNF (mBDNF) levels, increased AMP-activated protein kinase (AMPK) activation and decreased P70S6K activation, similarly to the situation in the liver under AL-HFD. High levels of mBDNF, decreased AMPK and increased P70S6K activation were found in the liver under KD and the brain under AL-HFD. RF-HFD led to a unique metabolic situation, in which high brain mBDNF levels correlated with increased AMPK and decreased P70S6K activation. In summary, in addition to the beneficial metabolic effects of RH-HFD, it leads to higher levels of BDNF in the brain, which may lead to the activation of protective mechanisms of neurons in neurodegeneration.