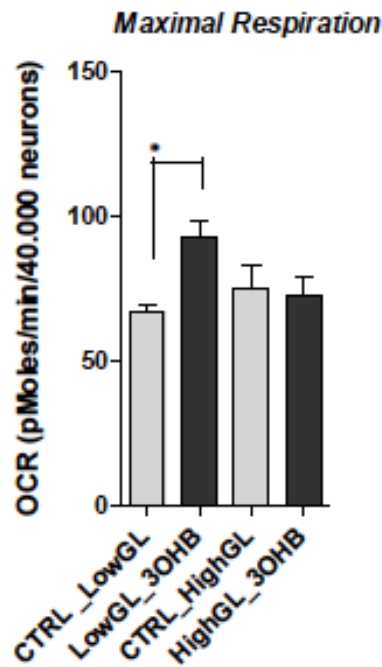


Supplemental Materials

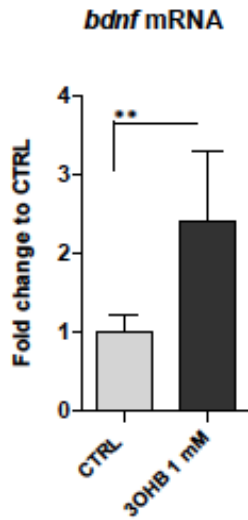
3-Hydroxybutyrate Regulates Energy Metabolism and Induces BDNF Expression in Cerebral Cortical Neurons

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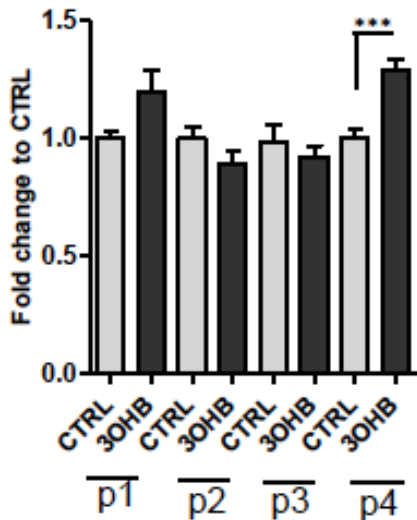
Supplemental Figures



S1. 3OHB induces mitochondrial respiration in low glucose (1mM) condition. 3OHB (1 mM) elevated the maximal oxygen consumption rate (OCR) in the primary cortical neurons only in low glucose condition versus Low Glucose CTRL * $p < 0.05$.

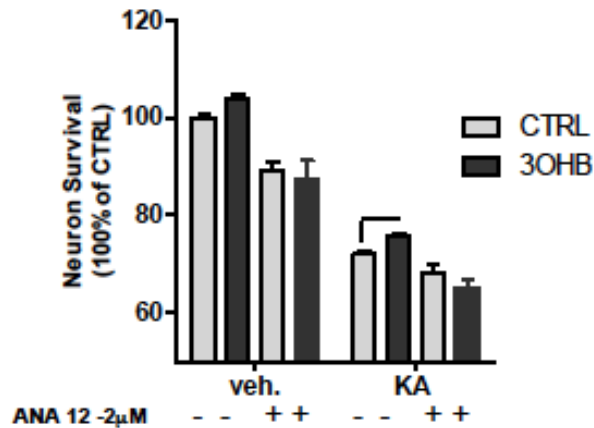


S2. 3OHB treatment increases BDNF expression in cultured hippocampal neurons Hippocampal neurons were incubated in medium containing a low (1 mM) concentration of glucose (GL) and were then exposed to 1 mM 3OHB or vehicle control (CTRL). Neurons were then harvested after 6 hours of 3OHB treatment for measurement of *Bdnf* mRNA levels. **p<0.01.

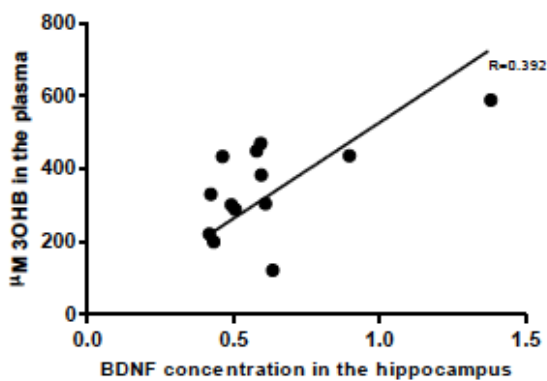


S3. 3OHB stimulates *Bdnf* promoter IV activity. HEK293 cells were co-transfected with *Bdnf* promoter I/II/III/IV-luciferase and pRL-TK and 24 hours later the cells were incubated in the absence

(CTRL) or presence (8 mM) for 6 h. The activities of each *Bdnf* promoters were measured as relative light units (RLU) expressed as fold change compared to the CTRL value (n = 4 separate cultures). ***p<0.001.



S4. Evidence that 3OHB protects neurons against kainic acid (KA)-induced cell death by mechanism that involves *Bdnf*. Cortical neurons incubated with without (CTRL) or with 8 mM 3OHB for 6 hours in the presence and the absence of TrkB inhibitor (ANA-12, 2 μM) then exposed to 100 μM kainic acid for 24 hours. 3OHB slightly prevented the KA-induced neuronal death. The protective effect of 3OHB was abolished in the presence of TrkB inhibitor (n = 3 separate cultures). *p<0.05.



S5. Plasma BDNF and 3OHB levels in sedentary and trained mice There was a significant correlation between the circulating levels in the 3OHB and the hippocampal BDNF levels R=0.392.