2k brief Mitochondrial disease
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High-resolution respirometry: Mitochondrial disease and neuroblastoma

Glutamate-Induced Deregulation of Krebs Cycle in Mitochondrial Encephalopathy Lactic Acidosis Syndrome Stroke-Like Episodes (MELAS) Syndrome Is Alleviated by Ketone Body Exposure

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Cells with the MELAS mutation (98 % MT) increased their routine (30 %) and their maximal (56 %) respiration capacity after treatment with Ketone Bodies (KB), compared to untreated mutant cells. KB exposure alleviates mitochondrial dysfunction.

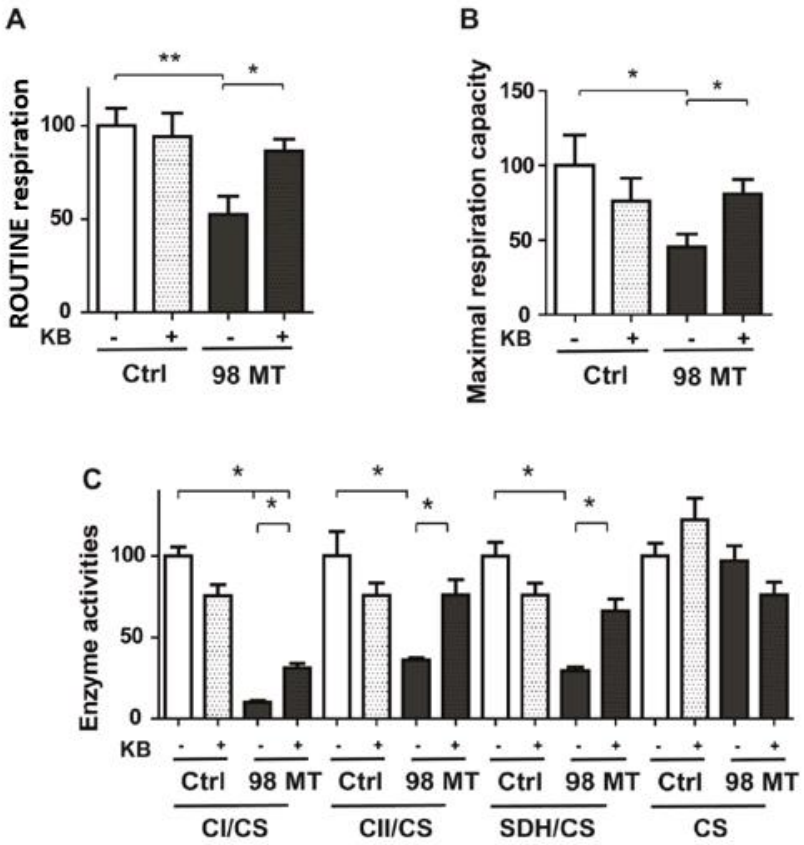

Figure 1. Treatment with ketone bodies improves mitochondrial respiration and enzyme activities in MELAS cells. (A) Oxygraphic measurements of ROUTINE **(B)** and maximal respiration capacity in Ctrl and 98 % MT cells, treated with (+) or without (-) KB for 48 h. **(C)** Enzyme activities of mitochondrial Complex I, II (CI, CII), and succinate dehydrogenase (SDH), relative to citrate synthase (CS) in control and 98% MT cells, treated for 48 h with or without KB. Results are presented as the mean ± SEM, relative to Ctrl cells, of at least 4 independent experiments. Statistical differences between 98 % MT and Ctrl cells are indicated with an asterisk (* $p < 0.05$; ** $p < 0.01$).

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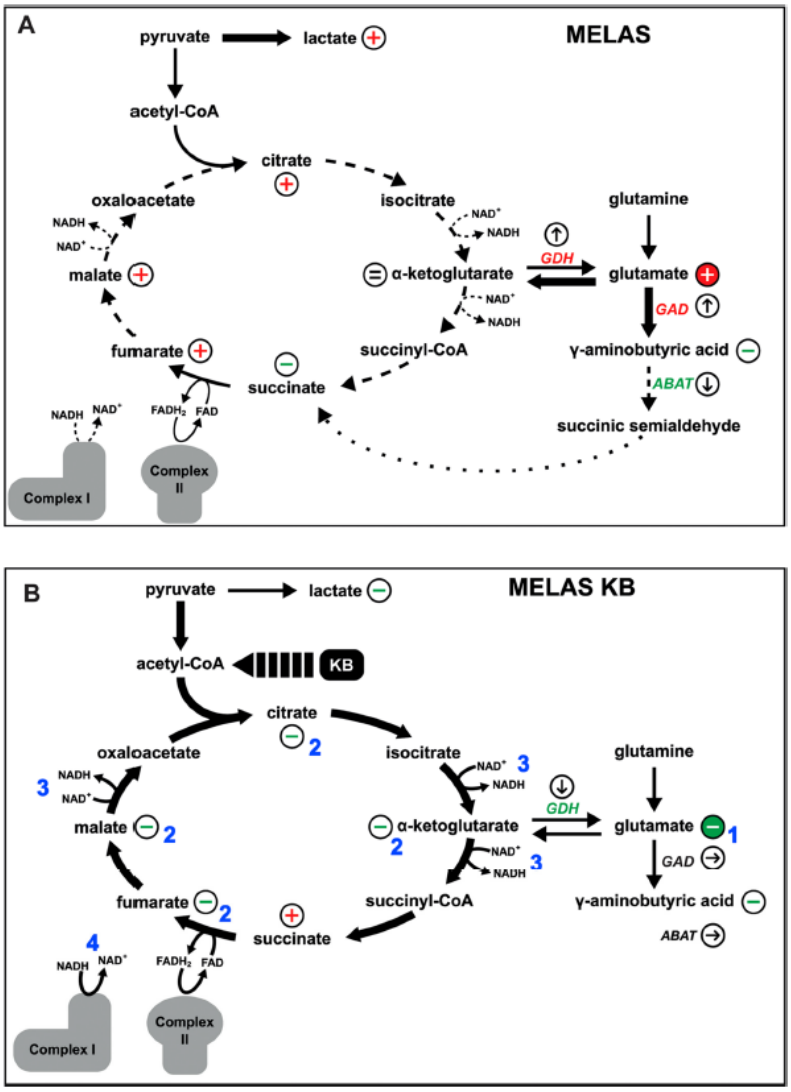

Figure 2. Graphical representation of metabolic pathways of MELAS cells (A) untreated (B) or treated with ketone bodies (KB). + metabolite increase; – metabolite reduction; = metabolite unchanged; ↑ increased gene expression; ↓ decreased gene expression. Metabolic consequences of KB treatment on mitochondrial metabolism are summarised in 4 main steps: 1) significant reduction of glutamate concentration; 2) reduction of the accumulation of TCA intermediates restoring the physiological function of the TCA cycle; 3) re-equilibration of the redox/NADH balance; 4) improving Complex I activity.

Metabolomic results showed a drastic increase in glutamate and glutamine in cells carrying the MELAS mutation compared to controls, together with the accumulation of TCA intermediates. After the treatment with KB, there was a switch from a glycolytic metabolism to a mitochondrial fatty acid oxidation, which led to restoration of TCA cycle function and an increase in oxidative metabolism. Therefore, a ketogenic diet is a promising approach towards alleviating mitochondrial dysfunction in MELAS disease.

Reference: Belal S, Goudenège D, Bocca C, Dumont F, Chao De La Barca JM, Desquiret-Dumas V, Gueguen N, Geffroy G, Benyahia R, Kane S, Khiati S, Bris C, Aranyi T, Stockholm D, Inisan A, Renaud A, Barth M, Simard G, Reynier P, Letournel F, Lenaers G, Bonneau D, Chevrollier A, Procaccio V (2022) Glutamate-induced deregulation of krebs cycle in mitochondrial encephalopathy lactic acidosis syndrome stroke-like episodes (MELAS) syndrome is alleviated by ketone body exposure. https://doi.org/10.3390/biomedicines10071665

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