Ketogenic flux from lipids and leucine, assessment in 3-hydroxy-3-methylglutaryl-CoA lyase deficiency.


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3-Hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase EC 4.1.3.4) catalyses the conversion of HMG-CoA to acetyl-CoA and acetoacetate. HMG CoA is formed both from leucine catabolism and by the HMG-CoA synthase reaction and plays a vital role in ketogenesis. 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency gives rise to 3-hydroxy-3-methylglutaric aciduria and affected patients are unable to synthesise acetoacetate or 3-hydroxybutyrate from fat catabolism or protein degradation. They excrete abnormally large amounts of HMG, 3-hydroxyisovalerate (3HV), 3-methylglutaconate and 3-methylglutarate in their urine [1,2]. Patients appear normal at birth but develop severe acidosis within a few months and frequently suffer from profound hypoglycaemia probably due directly to their inability to synthesise ketone bodies.

We have used H-1 m.r. spectroscopy to investigate a 12-year-old male patient when clinically stable and during an acute catabolic episode when 14 samples were collected during a 60 hour period of metabolic decompensation. A further sample was also taken one week later when the patient had stabilised.

To 0.5 ml aliquots of urine were added 50 μl of D2O containing 20 mM 3-trimethylsilyl)-2,2,3,3-tetradeuteropropionate (TSPd) for field locking and as an internal chemical shift reference respectively. The samples were run at room temperature in a Jeol GSX500 spectrometer using a single pulse sequence (30° pulse angle, 2.73 s acquisition time and a 5 s recycling time). Urinary metabolites were quantitated by measuring peak heights relative to the creatinine signals at 3.05 and 4.08 ppm.

The patient was admitted to hospital after 48 hours of vomiting with an intercurrent illness. He was semi-comatose and severely hypoglycaemic. He immediately received dextrose infusions and intravenous L-carnitine (4g) which has proved beneficial in a number of organic acidurias during metabolic perturbations [3]. The urinary concentrations of the major abnormal metabolites were elevated above the level seen during clinical stability and he had lactacidosis (lactate excretion 10.7 mmol/mol creatinine). Creatine also showed increased excretion as previously observed in this and other patients with organic acidurias during metabolic perturbations [3].

Over the first 24 hours after admission a further 2x1g doses of carnitine were given. During this time the metabolite excretion rose mostly due to increased excretion of 3HV which achieved a maximum of 6.1 mmol/mol Crn (a 10-fold rise over stable levels) 13 hours after admission. The excretion of 3HV also correlated well with the increase in creatine excretion which rose to a maximum of 1.7 mmol/mol Crn (normally <0.1 mmol/mol Crn) at the same time. This suggests that the elevated 3HV excretion may be ascribed to an increase in tissue protein, and specifically L-leucine, breakdown. Augmented release of creatine appears to be associated with muscle catabolism.

During the next 24 hours the patient was still semi-comatose and received another 2x1g doses of carnitine. The total urinary concentration of HMG metabolites changed very little but 3HV excretion decreased. In spite of an output of acetylcarnitine of 2 mmol/mol Crn, HMG excretion rose to more than 7 mmol/mol Crn (a nearly 10-fold rise) by 33 hours after admission. The rise in HMG excretion may be ascribed to an increase in attempted ketone body synthesis due to increased fat oxidation.

These results show that during the course of metabolic decompensation in this patient there was an initial increase in protein catabolism during the first 24 hours after admission. As the indicators of protein catabolism (creatinine and 3HV excretion) declined there was a concomitant rise in HMG excretion. This suggests a switch towards increased fatty acid oxidation and attempted ketogenesis despite the blood glucose being within normal limits during this period. Further study of such episodes is clearly of importance in understanding the role of ketogenesis in metabolic control and evaluation of optimal therapy.

One week after admission to hospital the concentration of all the major metabolites had returned to their baseline levels as seen before the episode and the patient was fully recovered.

Acknowledgements: We thank the University of London Intercollegiate Research Service at Birkbeck College for NMR facilities.

References.

Abbreviations used: HMG, 3-hydroxy-3-methylglutarate; 3HV, 3-hydroxyisovalerate; Crn, creatinine.