Abstract


In HepG2 Cells, Coexisting Carnitine Deficiency Masks Important Indicators of Marginal Biotin Deficiency.

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BACKGROUND: A large number of birth defects are related to nutrient deficiencies; concern that biotin deficiency is teratogenic in humans is reasonable. Surprisingly, studies indicate that increased urinary 3-hydroxyisovalerylcarnitine (3HIAc), a previously validated marker of biotin deficiency, is not a valid biomarker in pregnancy.

OBJECTIVE: In this study we hypothesized that coexisting carnitine deficiency can prevent the increase in 3HIAc due to biotin deficiency.

METHODS: We used a 2-factor nutrient depletion design to induce isolated and combined biotin and carnitine deficiency in HepG2 cells and then repleted cells with carnitine. To elucidate the metabolic pathogenesis, we quantitated intracellular and extracellular free carnitine, acylcarnitines, and acylcarnitine ratios using liquid chromatography-tandem mass spectrometry.

RESULTS: Relative to biotin-sufficient, carnitine-sufficient cells, intracellular acetylcarnitine increased by 90%, propionylcarnitine more than doubled, and 3HIAc increased by >10-fold in biotin-deficient, carnitine-sufficient (BDCS) cells, consistent with a defensive mechanism in which biotin-deficient cells transesterify the acyl-coenzyme A (acyl-CoA) substrates of the biotin-dependent carboxylases to the related acylcarnitines. Likewise, in BDCS cells, the ratio of acetylcarnitine to malonylcarnitine and the ratio of propionylcarnitine to methylmalonylcarnitine both more than tripled, and the ratio of 3HIAc to 3-methylglutaryl carnitine (MGc) increased by >10-fold. In biotin-deficient, carnitine-deficient (BDCD) cells, the 3 substrate-derived acylcarnitines changed little, but the substrate:product ratios were masked to a lesser extent. Moreover, carnitine repletion unmasked biotin deficiency in BDCD cells as shown by increases in acetylcarnitine, propionylcarnitine, and 3HIAc (each increased by >50-fold). Likewise, ratios of acetylcarnitine:malonylcarnitine, propionylcarnitine:methylmalonylcarnitine, and 3HIAc:MGc all increased by >8-fold.

CONCLUSIONS: Our findings provide strong evidence that coexisting carnitine deficiency masks some indicators of biotin deficiency and support the potential importance of the ratios of acylcarnitines arising from the acyl-CoA substrates and products for biotin-dependent carboxylases in detecting the biotin deficiency that is masked by coexisting carnitine deficiency.

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