Dichloroacetate stabilizes the mutant E1alpha subunit in pyruvate dehydrogenase deficiency.


Department of Clinical Neurology, University of Oxford, UK.

OBJECTIVE: To determine whether dichloroacetate (DCA) treatment can increase pyruvate dehydrogenase (PDH) activity in PDH-deficient cell lines harboring pathogenic mutations in the PDH E1alpha gene.

BACKGROUND: PDH deficiency is a nuclear-encoded mitochondrial disorder and a major recognized cause of neonatal encephalomyopathies associated with primary lactic acidosis. Over the last decade, DCA has been used therapeutically, but it has not been clear which patients might benefit. Recent studies suggest that chronic DCA treatment may act by increasing the stability of mutant E1alpha polypeptide. The relative effects of DCA treatment on PDH-deficient cell lines with E1alpha mutations primarily affecting polypeptide stability or catalytic activity were determined and the mechanism of enhancement of residual PDH activity explored.

METHODS: The effect of chronic 5-day DCA treatment on PDH activity was assessed in PDH-deficient cell lines containing the R378H, R141Q, K387(FS), and R302C E1alpha mutations. PDH subunit turnover and steady-state E1alpha levels before and after DCA treatment were measured in the R378H mutant line.

RESULTS: Chronic DCA treatment resulted in 25% (p = 0.0434), 31% (p = 0.0014) increases in PDH activity in the K387(FS) and R378H cell lines, both of which are associated with decreased mutant polypeptide stability. In the R378H mutant cell line, chronic DCA treatment increased steady-state E1alpha levels and slowed the rate of E1alpha turnover twofold. In contrast, PDH activity did not change in the chronically DCA-treated R302C mutant line, in which the mutant polypeptide has normal stability and reduced catalytic activity.

CONCLUSIONS: Chronic DCA treatment can increase PDH activity in PDH-deficient cell lines harboring mutations that affect E1alpha stability, suggesting a biochemical criterion by which DCA-responsive patients might be selected.

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