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Pathways of galactose metabolism by galactosemics: evidence for galactose conversion to hepatic UDPglucose.

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Abstract

To determine if classic galactosemics have residual galactose-1-phosphate uridyltransferase (GALT) activity to explain their considerable ability to oxidize galactose over 24 h, we devised a method for assessing their ability to form hepatic UDPglucose (UDPglu), an intermediate in the normal Leloir pathway of galactose metabolism. The protocol involved the single oral administration of 7 mg/kg [2-13C]galactose concomitant with multiple small doses of acetaminophen with measurement of the extent of labeling of urinary acetaminophen glucuronide, the glucuronide moiety being formed from hepatic UDPglu. We performed the study lasting 24 h in two normal subjects and three classic galactosemics, two homozygous for the Q188R mutation and one compound for the Q188R/K258N mutation. The labeling and total excretion of acetaminophen glucuronide was measured in urine by nuclear magnetic resonance techniques. Concomitant with determination of label in the glucuronide measurement was made of galactose oxidation to 13CO2 and the 13C enrichment of plasma glucose. All of the galactosemic patients formed 13C enriched acetaminophen glucuronide indicating that they had converted the labeled galactose to [13C]UDPglu and that residual GALT or another pathway that forms UDPglu is present in hepatic tissue. Compared to the normal whose glucuronide labeling was rapid and short-lived that of the galactosemics was delayed and extended for a long period over 10 h. The extent of isotopic enrichment of glucuronide by galactosemics was comparable to the normals, resulting in a much greater conversion of galactose to UDPglu by the galactosemics. The labeling of the UDPglu pool was reflected by the rate of 13CO2 formation being rapid in the normal with peak labeling at 2-3 h with total oxidation of over 70% in 24 h. The oxidation of the galactosemics was slow with a broad peak of 13CO2 at 10 h and a total excretion of 25-39% of the [13C]galactose administered. The normal subjects formed highly enriched plasma glucose within 30 min while no enrichment of plasma glucose was detected until after 300 min in galactosemics. The exact pathway(s) of galactose metabolism by galactosemics to UDPglu remain to be determined. Their delineation may contribute to new approaches to therapeutic strategies for this enigmatic disorder.

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