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Reye's syndrome and short-chain fatty acids

To the Editor: In measured plasma levels of short-chain fatty acids in Reye's syndrome, McArthur et al. found a significant increase only of propionic acid levels in patients with moderate or severe clinical signs, and of isovaleric acid concentrations in patients with moderate signs; isobutyric, n-butyric, n-valeric and caproic acid concentrations showed no elevation, but tended to values lower than those of controls. Of these six acids, increased levels of only isovaleric and propionic acids occur in disorders of biotin-dependent carboxylases. Isovaleric acid is elevated in cases of diminished activity of 3-methylcrotonyl-CoA carboxylase; propionic acid is elevated in propionyl-CoA carboxylase deficiency. The most prominent finding in a postmortem examination of mitochondrial liver enzymes in patients with Reye's syndrome was reduction of pyruvate carboxylase activity, another biotin-dependent carboxylase, and this could explain the lactic acidemia of Reye's syndrome. We found a marked reduction of plasma levels of biotin (caused by intake of anticonvulsants) and elevation of biotin-dependent short-chain fatty acids in the urine of seizure patients. Because Reye's syndrome is sometimes a fatal complication of anticonvulsant therapy, the possible relation between biotin status or biotin-dependent carboxylases should be considered in investigations of Reye's syndrome.

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References
Reply from the Authors: Krause, Berlit, and Bonjour offer an interesting explanation for the origin of short-chain fatty acidemia in Reye's syndrome (RS). To our knowledge, plasma biotin levels have not been measured in Reye patients, and the possibility of drug-induced biotin deficiency cannot be excluded. Nevertheless, some clinical and biochemical findings seem to be inconsistent with this mechanism as the primary cause of Reye's syndrome.

Clinically manifest biotin deficiency is rare, reported with prolonged parenteral alimentation or excessive ingestion of raw egg white. The typical manifestations (including seborrheic dermatitis, alopecia, and conjunctivitis) are slow to develop and respond promptly to biotin therapy. Conversely, Reye's encephalopathy is manifested by pernicious vomiting, behavior changes, and agitation that are sometimes followed by decorticate or decerebrate coma. Flaccid coma and death may result from brainstem compression due to intracranial hypertension.

Several chemical agents (including valproic acid) have been incriminated as causes of a "Reye-like syndrome." However, none of them has been documented as a cause of the salient ultrastructural, biochemical, and histochemical changes in liver that are characteristic of Reye's syndrome and which collectively define it as a distinct disease. In two patients with fatal hepatic failure after use of valproic acid, the liver injury differed from the lesion of RS on histopathologic examination. Hepatic pyruvate carboxylase activity is decreased in RS, but the biotin-independent hepatic mitochondrial enzymes, such as glutamic dehydrogenase and monoamine oxidase, are also decreased. These alterations are probably due to a general injury of hepatic mitochondria.

Given the fasted state of the RS patient before admission and the high rate of protein catabolism, the relatively modest elevations of short-chain fatty acids would be expected.

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References