

## CORRESPONDENCE

*To the Editor:* We read with interest the article by Plecko *et al.* in Pediatric Research (1). Plecko *et al.* show for the first time that exogenous administered DL- sodium  $\beta$ -hydroxybutyrate ( $\beta$ -OHB) can cross the blood brain barrier and be utilized by the brain as shown by MRS of the brain in two patients with hyperinsulinism in infancy (HI). Scientifically this is very interesting and reinforces findings from other studies that the brain can utilize alternative sources of fuels at the time of hypoglycemia.

From the clinical perspective this study raises some fundamental questions. These two patients were given relatively high doses of  $\beta$ -OHB for a period of 5 to 7 months and yet this treatment as expected had no impact on the natural history of HI. At the end of the study, the two patients were still severely hypoglycemic and requiring octreotide as well as frequent feeding to control the hypoglycemia. If the objective of the study was to show that DL sodium  $\beta$ -OHB can cross the blood brain barrier, this could have been done in a much shorter time interval.

Plecko *et al.* mention that oral administration of DL sodium  $\beta$ -OHB did not induce insulin secretion, but it is important to remember that both the patients were on treatment with octreotide at the time of oral  $\beta$ -OHB administration. Hence, it would be impossible to assess the insulin secretory responses to accumulation of DL sodium  $\beta$ -OHB in these patients.

Infants with HI also have an associated cardiomyopathy (2), which potentially increases the risk of  $\beta$ -OHB induced cardiac toxicity and arrhythmias. In addition, infants with HI have major feeding difficulties and have frequent vomiting with loss of 'orality' (2), which makes tolerating oral DL sodium  $\beta$ -OHB potentially difficult.

Thus far, mutations in four genes have been reported to cause HI (3). We have identified a patient with HI, whose primary genetic lesion is a point mutation in the short-chain 3-hydroxyacyl-CoA dehydrogenase gene (4). Others have identified mutations in this gene as a possible cause of HI (5), and recently we have identified another patient in which defective SCHAD activity may be the cause of hyperinsulinism. Metabolites measured/predicted in these patients would be L-3-hydroxybutyryl-carnitine, L-3-hydroxybutyrate and L-3-hydroxybutyryl-CoA. All of these metabolites would also be predicted to accumulate in patients given oral DL-3-hydroxybutyrate, and could in fact be responsible for triggering insulin secretion. Until the molecular basis of the hyperinsulinism in SCHAD deficient patients is understood, we would regard the administration of DL-3-hydroxybutyrate as potentially dangerous in the absence of octreotide, especially in patients for whom the genetic basis

of their HI is unknown (and who therefore could have deficiencies in SCHAD activity).

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### Response

We appreciate the discussion by Hussain concerning our article on the administration of DL sodium  $\beta$ -hydroxybutyrate in two cases with persistent hyperinsulinemic hypoglycemia of infancy (PHHI) as published in Pediatric Research (1).

The idea behind administration of DL sodium  $\beta$ -hydroxybutyrate was to provide an alternative energy fuel to protect the brain from damage potentially caused by recurrent hypoglycemic events. This is a neuroprotective approach, which is not expected to alter the natural history of hyperinsulinism. Therefore, with respect to insulin secretion and glucose homeostasis, preexisting treatment with octreotide and feeding schedules remained unchanged over the whole observational period.

The particular subject of this study was to show that oral DL sodium  $\beta$ -hydroxybutyrate accumulates in blood and crosses the blood brain barrier. The longer than necessary observation period allowed us to additionally evaluate possible side effects of DL sodium  $\beta$ -hydroxybutyrate. During the 5- to 7-month treatment period, octreotide demand and the frequency and degree of hypoglycemic episodes did not change. This strongly suggests that additional insulin secretion was not induced as a possible side effect of DL sodium  $\beta$ -hydroxybutyrate. Cardio-circulatory changes did not occur and preexisting ultrasonographic signs of hypertrophic cardiomyopathy even improved