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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 β-hydroxybutyrate (β-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 β-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 too show that DL sodium β-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 β-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 β-OHB administration. Hence, it would be impossible to assess the insulin secretory responses to accumulation of DL sodium β-OHB in these patients.

Infants with HI also have an associated cardiomyopathy (2), which potentially increases the risk of β-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 β-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).

Khalid Hussain
Simon Eaton
Peter Clayton
Institute of Child Health
Department of BEM
30 Guilford Street
London WC1N 1EH
K.Hussain@ich.ucl.ac.uk

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Response

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

The idea behind administration of DL sodium β-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 β-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 β-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 β-hydroxybutyrate. Cardiocirculatory changes did not occur and preexisting ultrasonographic signs of hypertrophic cardiomyopathy even improved

during the time course of observation in both patients. Cardiotoxicity as possible side effect of DL sodium β-hydroxybutyrate is thus unlikely. Vomiting or loss of "orality" was preexisting to the administration of DL sodium β-hydroxybutyrate and did not deteriorate upon treatment.

In our observational study, DL sodium β-hydroxybutyrate was administered as an ultima ratio in two infants with PHHI who suffered from recurrent hypoglycemic events despite extensive conventional treatment. Results are preliminary and further experimental and clinical studies are needed prior to general clinical application. In the light of the fact that short chain fatty acid oxidation defects such as SCAD and SCHAD deficiency may be associated with PHHI, we fully agree with Hussain *et al*. that patients who might potentially benefit from this treatment have to be selected carefully. Administration of DL sodium β-hydroxybutyrate in PHHI is complementary and is not a substitute of conventional therapy.

Barbara Plecko
Department of Pediatrics
University of Graz, Austria

Edith Schober
Department of Pediatrics
University of Vienna, Austria

Sylvia Stöckler-Ipsiroglu
Department of Pediatrics
University Hospital of Vienna
Waehringer Guertel 18-20
A-1090 Vienna, Austria
Tel: 43 1 40400 3210
Fax: +43 1 4063484
e-mail: stoeckler@metabolic-screening.at

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To the Editor: We read with interest the article by Schultz *et al*. (1), who present data on the neonatal inflammatory response.

As detection of intracellular cytokines may not necessarily correlate with extracellular cytokine concentrations, we do not totally agree with the authors' conclusions on the neonatal immune system extracted from these data.

As well, there may be concern about some methodical issues:

1. The authors stored blood samples for up to 24 hours at room temperature. Reinsberg *et al*. (2) showed that IL-8 concentrations in whole blood lysate increased significantly after 3 hours of storage at room temperature. The authors do not show data on the influences of sample storage.

2. Differences in storage time between the groups may have affected the results.

3. Van Langevelde *et al*. (3) reported a maximum endotoxin concentration of 18 pg/ml in adult febrile patients. In this study a maximal LPS stimulus of 30,000 pg/ml has been used. The effect on intracellular cytokine production may not reflect *in vivo* conditions.

4. It has been shown that labor induces cytokine production in term and preterm infants (4). Modification of cytokine synthesis by labor may differ in neonatal cells from preterm and term infants. The diminished spontaneous production of intracellular cytokines as well as the production after *ex vivo* stimulation in preterm infants <32 weeks gestational age could well have resulted from the 100% cesarean section rate in this group.

5. The authors demonstrate a dose related inhibition of *ex vivo* monocyte cytokine expression by incubation with dexamethasone. They do not comment on the possible effects of the different rates of corticosteroid pretreatment between the study groups (50%, 96%, 100%). There is no information on the number of doses and the type of steroid used for prophylaxis of RDS.

6. The diagnosis of neonatal infection has been based on single parameters. This is not a commonly used definition.

7. Anti-inflammatory activity has not been investigated. Data on IL-10 derived from different study designs are compared in the discussion.

On the background of these questions, the hypothesis of an enhanced neonatal inflammatory response remains at least debatable. Evaluation of imbalances of pro- and antiinflammatory components in neonatates may be more effective by investigation of a larger cytokine panel.

Jörg Dembinski
Daniela Behrendt
P. Bartmann
Department of Neonatology
University Bonn, Germany
Adenauerallee 199
D-53113 Bonn
Germany
jdembinski@uni-bonn.de

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Response

We would like to thank Dembinski and colleagues for the interest they have taken in our work. They raised concern about the method used and the conclusions drawn from our data. Until recently the neonatal inflammatory response was consid-