

LETTER TO THE EDITOR

New insights for glutaric aciduria type I

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doi:10.1093/brain/awl138

Received March 24, 2006. Accepted April 25, 2006.

Glutaric aciduria type I (GA-1) is due to recessively inherited glutaryl-CoA dehydrogenase (GCDH) deficiency and causes age-dependent susceptibility to acute striatal necrosis. A better understanding of the cellular and biochemical events underlying striatal damage will be required to prevent this devastating injury. The majority of past research effort has focused on the potential role of glutaric or 3-hydroxyglutaric acid (3-HGA) by exposure of cultured cells or brain slices to these metabolites *in vitro*, or their injection into rodent striatum (Kolker *et al.*, 2004). The GCDH-deficient mouse created by Koeller *et al.* (2002) does not develop striatal injury spontaneously. However, we have found that feeding the mouse a diet high in protein or lysine triggers an age-dependent severe neuropathology that mimics the human disease (Zinnanti *et al.*, 2006).

3-Hydroxyglutaric acid

Kolker *et al.* (2004) has noted that clarification is needed regarding 3-HGA concentrations in our diet-induced mouse model (Zinnanti *et al.*, 2006). We did in fact measure brain levels of 3-HGA in the GCDH-deficient mice on normal and high-lysine diets. Our initial measurements indicated that 3-HGA levels were similar to those previously reported (Koeller *et al.*, 2002). Subsequent measurements without using a lipid removal step showed reduced variability and revealed a significant increase in 3-HGA of ~90% in *Gcdh*^{-/-} mice on the lysine diet compared with the normal diet (manuscript in preparation). This finding by itself leaves open the possibility of a role for 3-HGA in the pathogenesis of GA-1.

It should be noted that the effects of 3-HGA *in vitro* have not been demonstrated at levels found in human GA-1 brain, making the importance of brain 3-HGA in the pathogenesis of GA-1 unclear. Furthermore, 3-HGA has been an incidental finding in other disorders that do not involve striatal necrosis (Molven *et al.*, 2004; Korman *et al.*, 2005), though levels in the various tissue compartments were not tested. Testing the toxicity of 3-HGA by its exogenous application at concentrations 10–100-fold greater than levels found in brains of GA-1 patients makes the assumption that 3-HGA accumulates in extracellular compartments at a substantial gradient to intracellular concentrations. In light of recent data showing low membrane permeability of glutaric acid and 3-HGA (Sauer *et al.*, 2006) as well as cerebrospinal fluid 3-HGA concentrations 100-fold lower than brain tissue levels (Schor *et al.*, 2002), such an extracellular accumulation seems unlikely.

Glutaric acid differences between *Gcdh*^{-/-} mice and human GA-1

Our studies have shown brain glutaric acid levels in GCDH-deficient mice on a normal diet to be 500 μM (Zinnanti *et al.*, 2006), similar to levels found in the original description of the GCDH-deficient mouse (Koeller *et al.*, 2002). Autopsy of human GA-1 brains has consistently shown higher brain glutaric acid levels of ~1250 μM (Leibel *et al.*, 1980; Goodman and Frerman, 1995). The failure of the GCDH mouse to develop striatal disease spontaneously may be due to this difference.

The current model of age-dependent encephalopathy using lysine feeding of weanling GCDH-deficient mice may

be used to resolve differences in developmental susceptibility in human GA-1. Most importantly, further use of the model may lead to therapeutic interventions for human GA-1.

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