Dietary lysine is a key phenotypic modifier of pyridoxine-dependent epilepsy: evidence from a mouse model

Hilal Al-Shekaili[1], Terri Petkau[1], Gabriella Horvath[3], Elizabeth Simpson[1,2], Jan Friedman[2], Clara van Karnebeek[4], Blair Leavitt[1,2].

(1)Centre for Molecular Medicine and Therapeutics, BC Children's Hospital, Vancouver, BC, Canada; (2)Dept. of Medical Genetics, University of British Columbia, Vancouver, BC, Canada; (3)Dept. of Pediatrics, BC Children's Hospital, UBC, Vancouver, BC, Canada; (4)Dept. of Pediatrics, Emma Children's Hospital, Amsterdam University Medical Centres, Amsterdam, The Netherlands

Background

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disease characterized by recurrent perinatal-onset seizures that are resistant to conventional anticonvulsant treatment but show remarkable response to pyridoxine (PN)[1]. PDE is caused by mutations in *ALDH7A1* which codes for an enzyme (antiquitin, ATQ) that functions within the cerebral lysine catabolism pathway (Fig. 1). Blockade of the ATQ-catalyzed step leads to the accumulation of lysine catabolites (Fig. 1). ATQ deficiency is thought to cause seizures because the lysine metabolite, P6C, condenses with and depletes pyridoxal 5'-phosphate (PLP), the cofactor required for neurotransmitter synthesis[1,2]. About 75% of PDE patients suffer neurodevelopmental disabilities even with adequate seizure control with PN treatment[3], which is thought to be caused by the build-up of lysine catabolites.

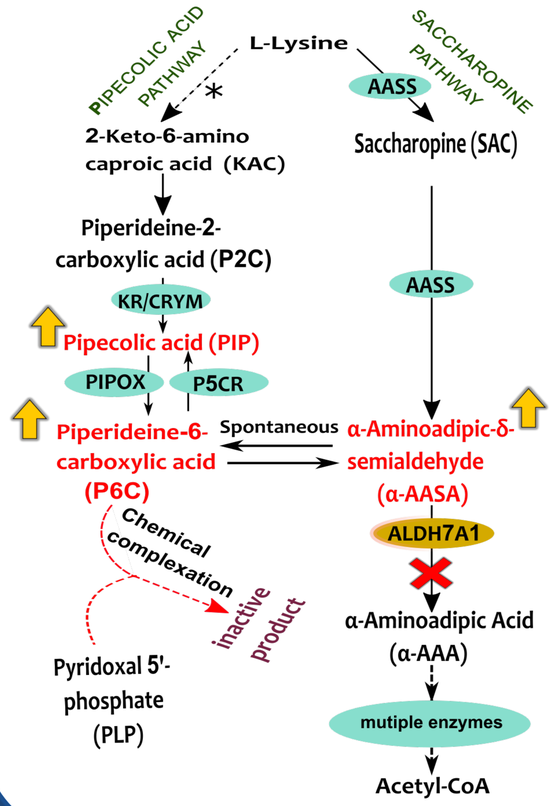

Fig. 1: Lysine catabolism pathway

Aim of the study

To study the effect of dietary lysine level on modulating the PDE phenotype in ATQ deficient mice.

Methods

We have generated a mouse model for PDE by targeted ablation of *Aldh7a1* in embryonic stem cells. To test the effect of lysine on the clinical phenotype, mice were fed two types of diets with varying levels of lysine: low (0.9%) and high (4.7%) lysine. The outcome was assessed by biochemical (measurement of lysine metabolite levels) and clinical (EEG and survival) analyses.

Results

Low Lysine diet causes accumulation of metabolites but no seizures

Aldh7a1-knockout (KO) mice fed the low lysine diet showed accumulation of the key PDE metabolic biomarkers in brain and liver (Fig. 2). However, *in vivo* EEG analysis revealed no seizures in these mice. PLP levels in brain of KO mice were not different from their wildtype (WT) littermates which could explain the absence of seizures

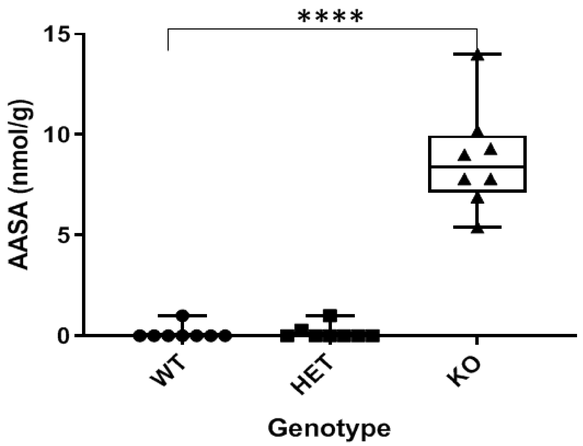

Fig. 2: Accumulation of the PDE biomarker, AASA, in brain of *Aldh7a1*-KO mice

High lysine diet induces seizures and rapid death in KO mice

Aldh7a1-KO mice fed the high lysine diet exhibited vigorous seizures and died within 2 – 2.5 days from the diet start (Fig. 3).

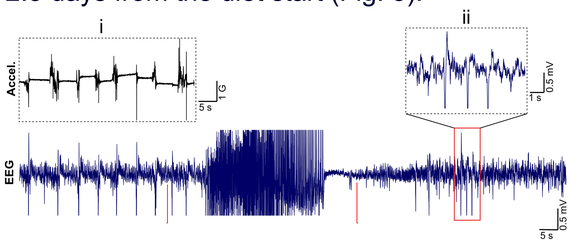

Fig. 3: EEG chromatogram from a KO mouse under high lysine diet showing generalized seizure.

High lysine diet causes robust biochemical changes in brain of KO mice

Mass spectrometry analyses revealed higher levels of lysine metabolites under the high lysine diet (Fig. 4) along with PLP deficiency (Fig. 5).

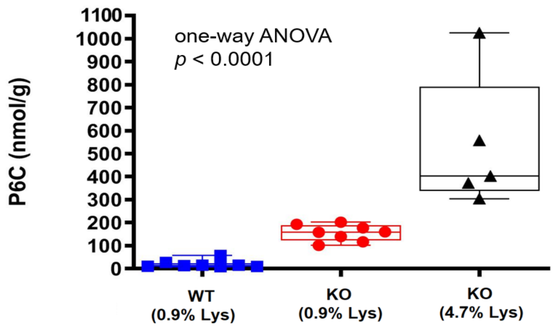

Fig. 4: High lysine diet causes higher P6C accumulation in brain of *Aldh7a1*-KO mice.

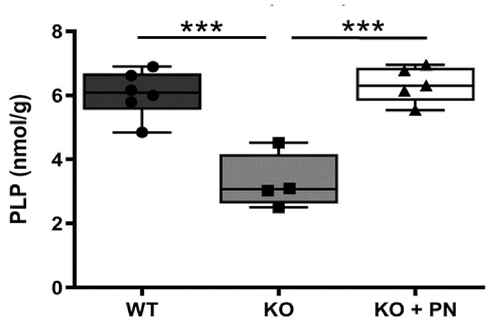

Fig. 5: High lysine causes PLP deficiency in brain of KO mice and PN rescues the phenotype.

PN rescues the phenotype

A cohort of KO mice receiving high lysine diet were also i.p. injected with PN which prevented seizures and death in these mice. PN treatment also restored PLP to normal levels in brain (Fig. 5).

Discussion

Our results indicate that high lysine diet can induce a PN-responsive seizure phenotype in Aldh7a1-deficient mice that recapitulates important clinical aspects of PDE. The results of high lysine exposure in these mice highlights dietary lysine as a potential environmental factor that influences the severity of the phenotype in ALDH7A1 deficiency. Adjunct dietary therapies like lysine-restricted diet have been tested in PDE patients and led to an improvement in the clinical outcome[4]. The detrimental effects of high lysine intake observed in our Aldh7a1-deficient mice strongly support the use of adjuvant therapies that aim to minimize lysine exposure in patients. The amenability of our mouse model to dietary manipulations is an important feature that makes this model suitable for studying the effect of novel dietary intervention therapies.

References

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