Streszczenie w języku angielskim

Biochemical characterization of the mouse model of Wilson's disease.

Introduction

Wilson's disease (WD) is a rare autosomal recessive genetic disorder characterized by impaired copper metabolism. The primary organs affected by the disease are the liver and the brain. The Jackson toxic milk mouse (txJ) is a mouse strain with a mutation in the *Atp7b* gene, homologous to the human *ATP7B* gene, mutations of which are responsible for WD.

Aim

The aim of the study was to describe the biochemical changes in selected structures (striatum, liver, heart, duodenum, eye) in txJ mice. Additionally, the study analyzed sex-related differences in the course of the disease in mice.

Methods

TxJ and control mice were sacrificed at 2, 4, 8, and 14 months of age. Total reflection X-ray fluorescence spectroscopy was used to determine elemental concentrations in organs. The biochemical composition of tissues was measured using Fourier-transform infrared spectroscopy. Additionally, hybrid multimodal microimaging of the brain was performed. Serum concentration of ceruloplasmin, neurofilaments, albumin, bilirubin, transaminases, and alkaline phosphatase were also assessed.

Results

Significantly elevated copper concentration was observed in the liver, striatum, eye, heart, and duodenum of txJ mice. Copper concentration disturbances were accompanied by changes in calcium content, especially in the liver and heart, and to a lesser extent in other organs. In the striatum of the oldest txJ mice, a lower lipid content and a higher proportion of saturated fats in the overall biochemical composition were observed. The secondary structure of striatal proteins was disrupted in txJ mice. In the liver, higher levels of saturated and oxidized fats were found. The biochemical composition of the txJ liver was dominated by significant disturbances resulting from improper folding of hepatocyte proteins due to secondary structure abnormalities. Neurofilament levels were elevated in the serum of 4-month-old txJ mice and

coincided with detectable biochemical changes in the liver, preceding the onset of elemental and biochemical disturbances in the striatum. The distribution of Cu and Zn in the brains of both groups was relatively uniform, with no dominance in any anatomical structure, but significant changes in the secondary structure of proteins were observed only in the striatum and thalamus of txJ mice. The disease course in female txJ mice differed primarily in hepatic concentrations of copper, calcium, and zinc, as well as copper and iron levels in the striatum. Lower plasma ceruloplasmin levels were also observed in females. The most pronounced sex-related differences in disease manifestation were observed at 4 months of age.

Conclusions

In txJ mice, the *Atp7b* gene mutation leads to changes in the elemental and biochemical composition of the liver and brain. As the disease progresses, the elemental composition of the heart, duodenum, and eye also changes. Liver damage associated with copper accumulation coincided with elevated serum neurofilament concentration. The course of the disease in txJ mice shows many similarities to the clinical picture and findings in human WD patients. The most pronounced sex-related differences at 4 months of age of txJ suggest a possible modifying influence of sex hormones.