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Folic acid as preventive therapy for hearing loss: effect of ototoxic drug consumption

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Abstract

Introduction: Age-related hearing loss (ARHL) is a sensory impairment, with a dramatic increase in its incidence, which is caused by genetic and environmental factors such as noise and ototoxic drugs. Recent studies correlated ARHL to elevated plasma homocysteine (Hcy) by folate deficiency, suggesting that reduction of Hcy levels by folate supplementation could potentially ameliorate ARHL.

Hyperhomocysteinemia (HHcy), a status that contributes to ARHL, may also arise from malfunction of Hcy remethylation by betaine homocysteine S-methyltransferases (BHMTs) and methionine synthase in the methionine cycle. The expression and/or activity of these enzymes may be altered by ototoxic drugs, including paracetamol (APAP).

Objective: To determine the effect of APAP in cochlear morphology and function of control and *Bhmt*$^{-/-}$ mice, and to analyze putative preventive effects of folic acid (FA) supplementation.

Materials and Methods: Two-month-old *Bhmt*$^{-/-}$ mice (n = 47), with greater dependence on folate metabolism for Hcy remethylation, and *Bhmt*$^{+/+}$ mice (n = 42) were fed control or FA supplemented diets for 30 days. The last day APAP (250 mg/kg) or placebo were injected intraperitoneally.

Hearing was evaluated by recording auditory brainstem responses (ABR) at the beginning of the experiment and after treatments. Picrosirius red staining was used for evaluation of the cochlear lateral wall cytoarchitecture. Plasma and hepatic metabolite levels were determined by HPLC or on Spinlab 100® autoanalyzer.

Results: Loss of *Bhmt* expression induced HHcy, but an impact on hearing acuity was not observed. Acute APAP administration did not induce ABR threshold shifts. However, following ototoxic treatment, changes of 5–17% in the areas of the stria vascularis and spiral ligament were detected between *Bhmt*$^{-/-}$ mice under different dietary treatments; cochlear structures of *Bhmt*$^{-/-}$ mice receiving APAP plus FA supplementation resemble those of the control group. APAP increases susceptibility to ototoxic damage in the presence of HHcy.

Discussion: BHMT plays a central role in cochlear methionine metabolism. FA supplementation modulates Hcy levels, contributing to a proper remethylation status that prevents ARHL.

Conflict of Interest

The authors declare no conflict of interest