Rescuing Noise-Induced Permanent Threshold Shift by D-Methionine in Guinea Pigs

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Abstract

Outcome Objectives: This study examined the effectiveness of D-Methionine (D-met) in rescuing a noise-induced permanent threshold shift (PTS) and cochlear biochemistry following noise exposure.

Methods: One hour after being exposed to continuous white noise at 105±2 dB SPL for 6 h, guinea pigs were treated 5 times at 12-hr intervals with 600 mg/kg D-met, compared with the control animals. The level of D-met in rescuing noise-induced hearing loss and the changes in cochlear biochemistry, including membranous Na+, K+-ATPase and Ca2+-ATPase, lipid peroxidation, and nitric oxide, were evaluated.

Results: Hearing acuity had no significant differences before and 14 days after noise exposure. Treatment with D-met before or after exposure to noise also reduced PTS in mice and chinchillas. The improvement effect of D-met on PTS was observed in greater following doses of 400 mg/kg for treatment with 200 or 100 mg/kg D-met, and treatment with 200 mg/kg D-met was shown to rescue NHI when administered up to 7 h after noise exposure. To the best of our knowledge, this was the first study to investigate the effects of post-exposure D-met treatment on NHI and to test the dose–response efficacy of the D-met treatment. We also examined the relationship between D-met treatment and changes in cochlear biochemistry in rescuing PTS.

Methods and Materials

Twenty-four guinea-pigs are randomly divided into four groups, comprising one saline-treated group and three D-met-treated groups. Each animal is exposed to a single continuous broadband white noise (125–15 kHz) at the level of 105±2 dB SPL for 6 h. Animals then receive sterile 0.9% saline alone, or different dose (200, 400 or 600 mg/kg) of D-met by intraperitoneal injection. In the D-met groups. Another six normal hearing guinea pigs were not exposed to noise and served as controls. All groups have ABRS performed 3 times before noise exposure, and 14 days after noise exposure. Each animal’s body weight was measured before and 14 days after the noise experiment. Mean body weights and ABRS before and 14 days after noise exposure in each group were compared using a two-tailed paired t-test. A one-way analysis of variance (ANOVA) followed by Bonferroni post hoc test was used to conduct multiple comparisons testing including D-met thresholds, Na+, K+-ATPase and Ca2+-ATPase activities, and levels of LPO and NO. Regression models are used to analyze the association between enzyme-specific activities and ABRS thresholds, LPO, or NO concentrations.

Results

Effects of D-met on general health status of guinea pigs

All of the animals in each of these groups survived until the end of the study period and the body weight change in each group is demonstrated in Fig. 1. All guinea-pigs appeared active and had a fair to good appetite during the experimental period. The mean body weight of guinea-pigs in all groups increased. The mean body weight change in each group was 49±7, 44±2, 31±13, 17±3, and 7±9 g for the groups of control, 0.9% saline, and D-met (200, 400, and 600 mg/kg), respectively. The increase in mean body weight of the control, saline, D-met (200 and 400 mg/kg) groups were significant before and after experiments (p<0.05). In the D-met 600 mg/kg group, the changes of mean body weight before and after experiments were statistically non-significant.

Effects of D-met on noise-induced PTS of ABRS

The mean ABRS thresholds and shifts for five study groups are summarized in Table 1 and Fig. 2. Compared with the mean PTS of the saline group, treatment with D-met 200 mg/kg did not significantly reduce the PTS. The mean PTS of the D-met 400 mg/kg group was significantly lower than that of the saline group but higher than that of the control group, indicating that D-met at this concentration had a partial rescue effect. The mean PTS of the D-met 600 mg/kg group did not significantly differ from that of the control group, reflecting that administration of D-met 600 mg/kg achieved a complete rescue response. D-Met caused a dose-dependent (200, 400, and 600 mg/kg) rescue from noise-induced PTS.

Effects of D-met on the noise-induced decrease in ATPase-specific activities

The mean Na+, K+-ATPase and Ca2+-ATPase in cochlear lateral walls for four treatment groups and the control group are summarized in Table 2 and Fig. 3. Compared with the mean ATPase enzyme activities of the saline group, administration of D-met 200 mg/kg did not significantly preserve both ATPase enzyme levels. D-Met at the dose of 400 mg/kg had a partial effect of preserving the two enzyme activities, since the mean enzyme concentrations of this treatment group were significantly higher than those of the saline group but lower than those of the control group. D-Met at the dose of 600 mg/kg achieved an optimal effect of preserving both enzyme activities, since the mean enzyme levels of this treatment group were not significantly different from those of the control group. D-Met rescue caused a dose-dependent (200, 400, and 600 mg/kg) attenuation of the noise-induced decrease of the Na+, and K+-ATPase, or Ca2+-ATPase activities in each group presented a significant negative association with its mean ABRS threshold (p<0.05).

Effects of D-met on the noise-induced increase in LPO and NO levels

The means of LPO and NO levels reflecting oxidative stress in guinea-pig cochlear lateral walls of various noise-exposed groups and the control group are displayed in Table 3 and Fig. 4. Compared with the saline group, administration of D-met 200 mg/kg did not significantly reduce both levels of LPO and NO. For the D-met 400 mg/kg group, both levels were significantly lower than those of the saline group but higher than those of the control group, reflecting that D-Met at this dose attenuated noise-induced oxidative stress to a partial extent. For the D-met 600 mg/kg group, both levels had no significant differences from those of the control group, indicating that D-met at this concentration achieved a total protective effect against oxidative stress. D-Met rescue caused a gradual decrease of the mean LPO and NO levels in D-met groups over concentration. Among various groups (N=5), the mean Na+, K+-ATPase, or Ca2+-ATPase activities in each group displayed a significant negative association with its mean ABRS threshold (p<0.05).

Conclusions

D-met significantly rescues noise-induced PTS in guinea pigs in a dose-dependent manner. The D-met-mediated improvement in auditory function correlated with a significant attenuation of increased oxidative stress and reduced ATPase activities.

References