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The Effect of Alcohol Dehydrogenase Isozymes on Alcoholic Liver Disease and Alcoholic Osteoporosis

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Alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde during alcohol metabolism. ADH has several isozymes, of which ADH1 is a key enzyme responsible for 80% of ethanol oxidation. ADH3, with the highest K_m of ethanol among all ADH isozymes, participates in systemic alcohol metabolism in chronic alcohol consumption (CAC) or high blood alcohol concentration (BAC). In addition, ADH3 is the ancestral enzyme distributed in almost all mammalian tissues and involved in S-nitrosoglutathione (GSNO) reducing activity. *Adh3* null mutant mice reportedly exhibit bronchial asthma due to GSNO accumulation¹ or decreased DNA repair ability by promoting S-nitrosylation of DNA repair proteins². We hypothesize that alcohol-related organ disorders might be due to ADH3 participation in the local metabolism of ethanol, which may generate secondary metabolites, resulting in tissue damage. In addition, the primary physiological role of ADH3 may be inhibited by CAC due to its participation in alcohol metabolism. We investigated the effects of ADH1 and ADH3 on alcoholic liver disease and alcoholic osteoporosis during CAC to clarify their involvement in ADH pathogenesis. First, nine-week-old male mice of different ADH genotypes (WT, *Adh1*^{-/-}, and *Adh3*^{-/-}) were administered 10% ethanol solution for 1 month, followed by acute ethanol administration (4.0 g/kg). BAC was measured, and the alcohol elimination rate (AER) was calculated. Furthermore, the liver content was evaluated by enzyme-linked immunosorbent assay (ELISA). CAC increased AER in all ADH genotypes, indicating that the mice acquired metabolic tolerance to ethanol in the early period of CAC. The increased ADH1 content correlated with AER in WT mice. Similarly, the increased ADH3 content also correlated with AER in both WT and *Adh1*^{-/-} mice. We conclude that ADH1 contributes to metabolic pharmacokinetics of CAC with increased AER by increasing the enzyme content³. ADH3 also contributes to increased AER by an adaptive increase in the enzyme content³. ADH3 regulates both adipogenesis and osteogenesis through the denitrosylation of peroxisome proliferator-activated receptor γ (PPAR γ). We also investigated the contribution of ADH3 to the development of alcoholic osteoporosis during CAC. For this, nine-week-old male mice of different ADH genotypes (WT and *Adh3*^{-/-}) were administered 10% ethanol solution for 12 months. The mice in the control group were provided only water for 12 months. The femurs were evaluated by computed tomography-based bone densitometry. The mRNA levels of ADH3 were measured in the WT mice by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). The *Adh3*^{-/-} control mice exhibited increased activities of both osteoblasts and osteoclasts and lower bone masses than the WT control mice. CAC exhibited no remarkable changes in osteoblastic and osteoclastic activities, but

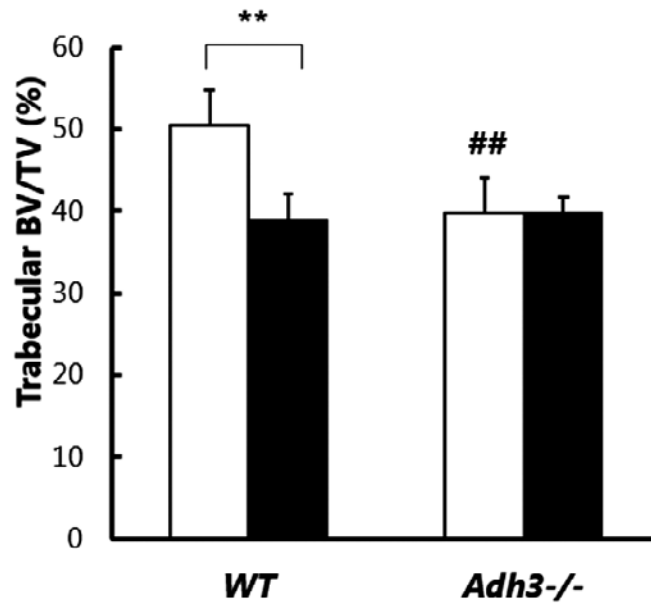


Fig. 1 Computed tomography-based bone densitometry of the trabecular BV/TV at the proximal portion of the growth plate. The white bars represent the mice that were provided water (control groups), and the black bars represent the mice that were administered 10% ethanol (w/v) solution for 12 months (ethanol groups). ** $p < 0.01$ between the control and ethanol group as assayed by the Student-Newman-Keuls method. ## $p < 0.01$ between the WT control mice and *Adh3*^{-/-} control mice as assayed by the Student-Newman-Keuls method. BV/TV, bone volume/total volume; WT, wild-type mouse (*C57BL/6N*); *Adh3*^{-/-}, *ADH3* knockout mouse.

decreased bone masses were observed in WT mice despite an increase in the mRNA levels of ADH3. Conversely, bone masses in the *Adh3*^{-/-} control mice were not reduced after CAC (**Fig. 1**). We conclude that ADH3 could prevent osteoporosis development in normal ADH genotypes with no alcohol ingestion. However, ADH3 contributes to the development of alcoholic osteoporosis under CAC by participating in alcohol metabolism, increasing metabolic toxicity, and lowering GSNO reducing activity.

These studies indicate that ADH acquires metabolic tolerance in early CAC and is actively involved in alcohol metabolism. With regard to ADH3, the cellular physiological functions of various organs might collapse, and various disorders might appear in cases of CAC.

References

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