Arylacetamide deacetylase knockout mice are sensitive to ketoconazole-induced hepatotoxicity and adrenal dysfunction

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Abstract

Background and Purpose Orally administered ketoconazole rarely induces liver injury and adrenal dysfunction. *In cellulo* studies showed that a metabolite formed by arylacetamide deacetylase (AADAC)-mediated hydrolysis is relevant to ketoconazole-induced cytotoxicity. This study tried to examine the significance of AADAC in ketoconazole-induced toxicity *in vivo* using Aadac knockout mice. Experimental Approach Wild-type and *Aadac* knockout mice orally received 150 or 300 mg/kg/day ketoconazole, and plasma parameters, the concentrations of ketoconazole and *N*-deacetylketoconazole in plasma and tissues, and hepatic mRNA levels of immune- and inflammatory-related factors were measured. The effects of pretreatment with corticosterone (40 mg/kg, *s.c.*) on ketoconazole-induced liver injury were also examined. Key Results In a study of a single oral administration of 150 mg/kg ketoconazole, the area under the plasma concentration curve values of ketoconazole and *N*-deacetylketoconazole in *Aadac* knockout mice were significantly higher and lower than those in wild-type mice, respectively. With the administration of ketoconazole (300 mg/kg/day) for 7 days, *Aadac* knockout mice showed higher mortality (100%) than wild-type mice (42.9%), with significantly higher plasma alanine transaminase and lower corticosterone levels, representing liver injury and adrenal dysfunction, respectively. In *Aadac* knockout mice, hepatic mRNA levels of immune- and inflammatory-related factors were increased by the administration of ketoconazole, and the increase was restored by the replenishment of corticosterone, which shows anti-inflammatory effects. Conclusion and Implications *Aadac* defects exacerbated ketoconazole-induced liver injury by inhibiting glucocorticoid synthesis and enhancing the inflammatory response. This *in vivo* study revealed that the hydrolysis of ketoconazole by AADAC can mitigate ketoconazole-induced toxicities.

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