RESVERATROL ATTENUATES SOME FORMS OF DIOXIN TOXICITY IN MICE

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Abstract

The protective effect of resveratrol against toxicities induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) was studied in C57BL/6J mice. Resveratrol partially protected mice from body weight loss caused by TCDD, although hepatomegary and thymic atrophy were not improved by the polyphenol. Hepatic lipid accumulation induced by TCDD was also notably decreased by co-treatment with resveratrol. To seek the mechanisms of such effects, ethoxyresorufin *O*-deethylase activity and the content of thiobarbituric acid-reactive substances were measured. However, resveratrol co-treatment did not show any significant effect on both parameters. The data obtained suggest that resveratrol exhibits a protective effect against some forms of dioxin toxicity, although the mechanism remains to be clarified.

Introduction

Dioxins are widespread, persistent and highly toxic environmental pollutants. Among dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is the most toxic congener and has been widely investigated as a prototype for this class of chemicals. Dioxins are known to produce a wide spectrum of effects including lethality, wasting syndrome, atrophy of thymus and spleen, tumor promotion, immunosuppression, teratogenicity, and endocrine changes in mammal.[1,2] Although dioxins exert their toxicities through interaction with aryl hydrocarbon receptor (AhR),[3,4] the mechanism of dioxin toxicity following AhR activation has not been elucidated.

Resveratrol (trans-3,4',5-trihydroxystilbene) is well-known as a phenolic ingredient in red wine. Epidemiological studies have suggested that the consumption of wine reduces the incidence of mortality and morbidity from coronary heart disease.[5] This is so-called 'French Paradox', and resveratrol is assumed to be one of the key ingredients having a protective effect . In addition, Casper et al. have recently demonstrated that resverastrol antagonizes TCDD-dependent activation of AhR.[6] Therefore, it is reasonably expected that

resveratrol has the merit for testing as a possible prophylactic agent against aryl hydrocarbon-induced toxicities. To address this issue, we examined the effects of resveratrol on the acute toxicity of TCDD. In this study, our results show that resveratrol is able to reduce some forms of TCDD toxicity such as wasting syndrome.

Materials and Methods

Male C57BL/6J mice (4 weeks-old) were purchased from CLEA Japan (Tokyo, Japan), and acclimatized for one week prior to treatment. Throughout the experiment, mice were allowed to access to food and water *ad libitum*. Mice were randomly divided to groups (8 mice per group) by body weight, and they were orally administrated resveratrol (20 mg/kg body weight) or vehicle. Then, 90 minutes after treatment, TCDD (100 μg/kg) or vehicle was given by gavage. After the initial treatment on day 0, resveratrol was administrated once a day at same dose for 28 days. During the study, the body weights of all mice were measured before administration. Thirty minutes after the last administration of resveratrol, organs of all mice were removed and weighted. Homogenate and 9,000 x g supernatant from 5 mice were prepared with 1.15% KCl. Ethoxyresorufin *O*-deethylase (EROD) activity and the content of thiobarbituric acid reactive substances (TBARS) were measured according to the method of Burke and Mayer[7] with minor modification and Okawa et al.,[8] respectively. Liver slices were prepared from other 3 mice, and then stained with Oil Red to investigate the accumulation of lipid drop.

Results and Discussion

One day after TCDD treatment, significantly loss of body weight gain was observed. The marked suppression of body weight gain in mice continued until the last administration. Co-treatment with resveratrol apparently prevented TCDD-induced body weight loss, although the effect was incomplete. In addition, no mice died in co-treated group, while 1 out of 8 mice died at day 27 in TCDD-treated group. On the other hand, resveratrol has no effect on hepatomegary and thymic atrophy induced by TCDD. The hepatic EROD activity and TBARS content were significantly increased by the treatment of TCDD against control. However, both parameters remained unchanged following co-treatment with resveratrol, although a slight decrease was seen in EROD activity. Hepatic lipid drops stained with Oil Red were notably decreased in co-treated group compared with TCDD-treated group. It is, therefore, suggested that resveratrol has an effect to attenuate some forms of dioxin toxicity. As mentioned above, co-treatment with resveratrol did not cause any change in EROD activity and

TBARS contents. Thus, it is one of the possibilities that resveratrol exerts the protective effect by a mechanisms distinct from antagonizing AhR. In addition, the half-life of resveratrol in mice should be considered because it has been reported that resveratrol is rapidly metabolized and disappeared within 3 hours from mouse serum.[9] Although this study could not clarify the reason explaining the protective effect of resveratrol, our results provided a new insight into the development of therapeutic and preventive approach for dioxin toxicity.

References

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