IN VIVO EFFECTS OF PANAX GINSENG EXTRACTS ON THE CYTOCHROME P450-DEPENDENT MONOOXYGENASE IN THE LIVER OF GUINEA PIG EXPOSED TO 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN

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Introduction

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is an extremely potent environmental contaminant that produces a wide range of adverse biological effects. CYP1A1 and CYP1A2 are two of the most well characterized TCDD-inducible cytochrome P450 isozymes, and current dose-response models of TCDD action in the liver are based on the analysis of TCDD-induced expression of CYP1A1 and CYP1A2[1,2].

From ancient times Korean ginseng (Panax ginseng C.A. Meyer) has been used to prevent and treat a variety of pathological conditions, particularly those associated with aging. Recently, it has been found that ginseng protects human body from toxic substances as well as other human diseases by several different mechanisms. However, there have been less studies on prevention or therapy against TCDD toxicity. Therefore, we investigated *in vivo* effect of panax ginseng extracts on the cytochrome P450-dependent monooxygenase system in the liver of guinea pig exposed to TCDD.

Materials and Methods

Sixty male Guinea pigs (Hartley strain, 190-210g) were maintained under controlled conditions of 23±1℃, RH 40-60%, in a 12hr-light/dark cycle. Water extracts of panax ginseng were kindly gifted by Dr. K. J Choi, Korea Ginseng & Tobacco Research Institute, Korea. The animals were allowed free access to solid rabbit food, fresh cabbage, and tap water. The animals were divided into four groups. After acclimation for 1 week, TCDD treatment group was administered with a single intraperitoneal dose of 1μg TCDD/kg body weight. Group of ginseng extract treatment alone received 100 mg/kg/day for 14 days from 1 week after single i.p injection of vehicle. Group of both treatment of TCDD and ginseng extract received 100 mg/kg/day for 14 days from 1 week after single i.p injection of TCDD. Control group received the same amount of the vehicle alone. At 4 weeks after dosing, the animals were sacrificed, livers removed, and quickly frozen in liquid nitrogen and stored at –70℃ until further processing.

Microsomal fractions were prepared by differential centrifugation as described previously[3]. Contents of P450[4] and b_5[5] were measured as described previously, respectively. NADPH-P450 reductase activity was measured by monitoring the reaction rate of P450 at 37℃ for 3-4 min[6]. Microsomal lipid peroxidation was determined as the content of thiobarbituric acid reactive substances (TBARS) as described previously[7], using malondialdehyde as the standard. 7-Ethoxycoumarin *O*-deethylase (EROD)[8] and benzphetamine *N*-demethylase (BPDM)[9] activities were assayed as previously described, respectively. Protein was determined by the method of Lowry *et al*[10], using bovine serum albumin as the standard.

Results and Discussion

We examined the effects of ginseng extract on the hepatic contents of P450 and b_5 in the TCDD-exposed guinea pig. As shown in Fig. 1, ginseng extract remarkably inhibited P450 contents which was induced by TCDD, but had no effect on the b_5 content. These results suggest that TCDD is a strong inducer of CYP, whereas ginseng extract is an inhibitor or inactivator of CYP. When compared with that of control, NADPH-P450 reductase activity was remarkably induced by TCDD, which was inhibited by ginseng extract. However, ginseng extract itself had no effect on the activity of the NADPH-P450 reductase (Fig. 2). However, there were no changes in the activity of b_5 reductase of the guinea pig liver by TCDD and/or ginseng extract administration (data not shown).

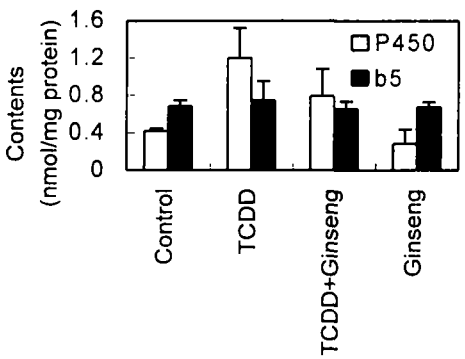

Fig. 1. Effect of ginseng extract on the hepatic contents of P450 and b5 in the guinea pig treated with TCDD.

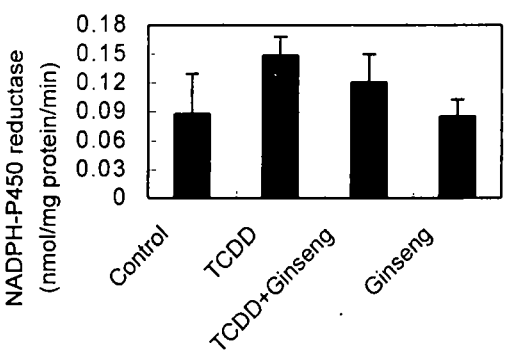

Fig. 2. Effect of ginseng extracts on the activity of NADPH-P450 reductase in the hepatic microsomes of the guinea pig exposed to TCDD

When compared with that of control, ECOD acitivity was increased by TCDD administration, but was rather decreased by ginseng extract dose (Fig. 3). This result suggests that TCDD is an inducer of CYP1A, but ginseng extracts may be rather inhibitor or inactivator of the enzyme in the

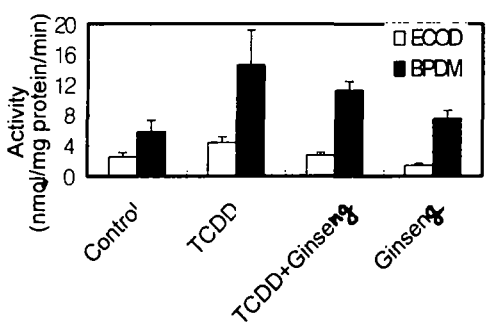

Fig. 3. Effect of ginseng extract on the activities of ECOD and BPDM in the hepatic microsomes in the of the guinea pig treated with TCDD.

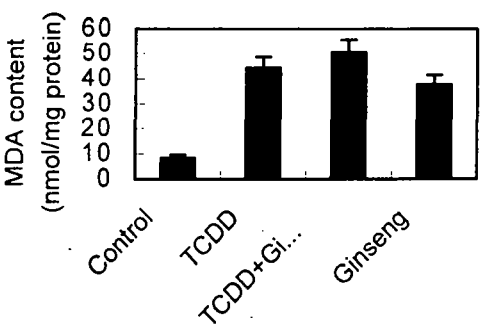

Fig. 4. Effect of ginseng extract on the production of lipid peroxidation in the hepatic microsomes of the guinea pig treated with TCDD.

liver microsomes of guinea pig. Further studies are necessary for clear resolution of the latter suggestion, inhibitor or inactivator.

As shown in Fig. 3, TCDD administration also remarkably induced BPDM activity and ginseng extract slightly increased the enzyme activity, but the induction by ginseng extract was statistically not significant. The result shown in Fig. 3 indicates that ginseng extract exerts different roles depending on the P450 isozymes. On the other hand, administration of ginseng extract inhibited TCDD-induced BPDM activity in the guinea pig liver microsomes. From these results, it is suggested that ginseng extract may act as an inhibitor of CYP1A rather than as an inhibitor of CYP2B.

Lipid peroxidation was measured in the livers of guinea pigs that treated with TCDD and/or ginseng (Fig. 4). When compared with control, TCDD and ginseng extract induced the generation of TBARS by 5.5 and 4.6 fold, respectively. Ginseng extract further stimulated the promotion of TBARS contents generated by TCDD. This result may suggest that inhibition of P450 contents by ginseng extract is associated with the promotion of TBARS generation in the liver of guinea pig.

Acknowledgments

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