Genetic Evidence of Resistance to Cadmium Toxicity in Wistar-Imamichi Rats

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Resistance to the toxicity of cadmium (Cd) was examined in male Wistar-Imamichi (Wistar-IM) and Fischer 344 (Fischer) rats. The Wistar-IM strain was confirmed to exhibit strong resistance compared to the Fischer strain. The resistance in first filial (F1) males was intermediate between that in Wistar-IM and that in Fischer males. The data from reciprocal crosses indicate that the strong resistance to Cd toxicity in male Wistar-IM rats is autosomal and inherited as an incompletely dominant phenotype.

Key words —— cadmium, Wistar-Imamichi rat, resistance, first filial progeny, incompletely dominant phenotype

INTRODUCTION

The heavy metal cadmium (Cd) is an industrial and environmental pollutant. Acute administration of Cd often induces lethal toxicity in mice and rats.[1–4] This may be because the metal is rapidly distributed into the liver of these laboratory animals and causes severe hepatotoxicity.[5,6] Recently, Harstad and Klaassen[7] have reported a strain difference of Cd-induced hepatotoxicity in Fischer 344 (Fischer) and Sprague-Dawley (SD) rats: administration of Cd at a dose of 2.0 mg/kg causes extensive hepatotoxicity in Fischer rats, but only minimal hepatotoxicity in SD rats. However, the genetic basis of resistance or susceptibility to Cd-induced hepatotoxicity remains to be elucidated.

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Our previous paper[8] has demonstrated that male Wistar-Imamichi (Wistar-IM) rats, derived from the Wistar strain, exhibit a strong resistance to the toxicity of Cd compared to male Wistar, Fischer and SD rats. The Wistar-IM strain, like the Fischer strain, is taken as an inbred rat strain.[9] Thus, the Wistar-IM strain is useful for analyzing genetically resistance to Cd toxicity. The purpose of the present study is to examine the toxicity of Cd in male rats of the first filial (F1) progeny generated by mating the Wistar-IM strain with the Fischer strain. We provide evidence that the strong resistance to the lethal toxicity of Cd segregates as an incompletely dominant phenotype in reciprocal crosses between the two rat strains.

MATERIALS AND METHODS

Materials —— Cadmium chloride ($CdCl_2$) was purchased from Sigma (St. Louis, MO, U.S.A.). All other chemicals were of reagent grade.

Animals and Treatment —— Male and female Fischer rats at 8 weeks of age were purchased from Japan SLC (Shizuoka, Japan). Male and female Wistar-IM rats at 8 weeks of age were obtained from the Imamichi Institute for Animal Reproduction (Ibaraki, Japan). All animal experiments were undertaken in compliance with the guideline principles and procedures of Kumamoto University for the care and use of laboratory animals. Reciprocal crosses, (male Wistar-IM × female Fischer) and (male Fischer × female Wistar-IM), were performed to generate $F1_a$ and $F1_b$ progeny, respectively. The male $F1_a$ and $F1_b$ rats were raised to 8 weeks of age under controlled lighting, temperature and humidity. $CdCl_2$ dissolved in approximately 0.5 ml of saline solution was subcutaneously injected into male Wistar-IM, Fischer, $F1_a$ and $F1_b$ rats at 8 weeks of age. The doses were 2.5, 3.5, 5.0 and 8.0 mg of Cd per kg of body weight. The male animals had free access to a diet of standard laboratory chow and water. The survival rate (%) for 7 days was observed.

RESULTS

Resistance to Cd Toxicity in Male Wistar-IM and Fischer Rats

Figure 1 shows the survival rate in male Wistar-IM and Fischer rats treated with Cd at various doses. All rats of the Fischer strain died one day after treat-

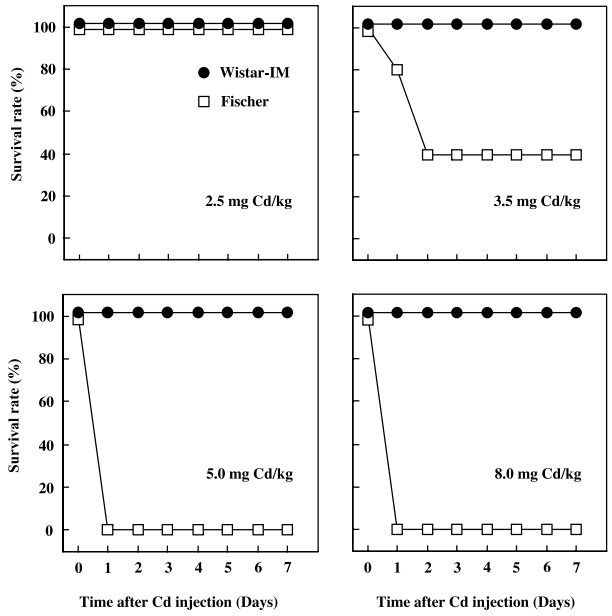

Fig. 1. Toxicity of Cd in Male Wistar-IM and Fischer Rats

The doses of Cd were 2.5, 3.5, 5.0 and 8.0 mg/kg body weight. The experiment was performed using 5 rats of each strain. The toxicity of Cd is expressed as the survival rate (%).

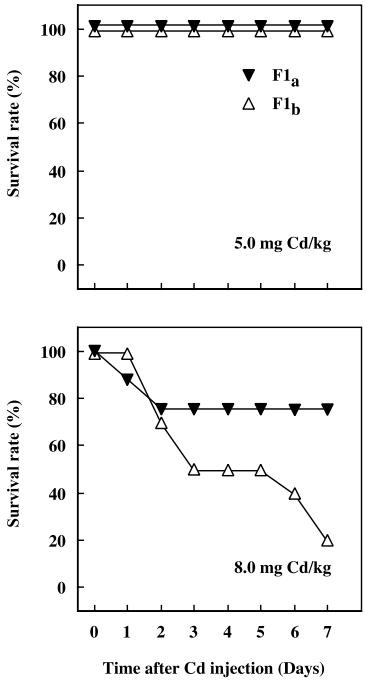

Fig. 2. Toxicity of Cd in Male $F1_a$ and $F1_b$ Progeny

The doses of Cd were 5.0 and 8.0 mg/kg body weight. The experiment was performed using 4–10 rats of each progeny. The toxicity of Cd is expressed as the survival rate (%).

ment with Cd at a dose of 5.0 mg/kg body weight. On the other hand, all rats of the Wistar-IM strain survived for 7 days after treatment with Cd at a dose of 8.0 mg/kg body weight.

Resistance to Cd Toxicity in $F1_a$ and $F1_b$ Males

The resistance to the lethal toxicity of Cd was examined in male $F1_a$ and $F1_b$ rats. As shown in Fig. 2, all rats of the $F1_a$ and $F1_b$ progeny, like male Wistar-IM rats, survived for 7 days after treatment with Cd at a dose of 5.0 mg/kg body weight. However, when the dose was increased to 8.0 mg/kg body weight, 25% of the $F1_a$ progeny and 80% of the $F1_b$ progeny died within 7 days after the treatment. These results indicate that the resistance to Cd toxicity in the reciprocal F1 ($F1_a$ and $F1_b$) progeny is intermediate between that in Wistar-IM and that in Fischer rats (see Fig. 1).

DISCUSSION

The data from reciprocal crosses of Wistar-IM and Fischer rat strains demonstrate that the strong resistance to the lethal toxicity of Cd in male Wistar-IM rats is autosomal and inherited as an incompletely dominant phenotype. However, when Cd was used at a dose of 8.0 mg/kg, the survival rate in male $F1_a$ progeny from the male Wistar-IM × female Fischer cross was somewhat different from that in male $F1_b$ progeny from the male Fischer × female Wistar-IM cross. Therefore, we cannot exclude at this time the possibility that the Cd resistance might be modified by either an X-linked or imprinted autosomal gene.

Because Cd initially accumulates in the liver, acute exposure to toxic doses causes damage to the liver. Thus, the hepatic uptake of Cd in the resistant strain is likely to be inherently different from that in the sensitive strain. In fact, our preliminary experiments have shown that in male rats, the Cd content of the liver after administration is significantly lower in the Wistar-IM than Fischer strain (data not shown). Transporters are an important factor in the uptake of endogenous and exogenous compounds in mammalian cells.[10] Several metal transporters are known to play a role in the cellular uptake of Cd.[11–15] For example, divalent metal transporter 1 (DMT1) involved in iron uptake from the intestine is the first mammalian metal transporter found that can facilitate the cellular uptake of Cd.[11,12] Recently, Himeno *et al.*[14] have revealed that a manganese (Mn) transport system is used for the cellular uptake of Cd and the uptake rate of Mn is markedly reduced in Cd-resistant cells. Based on these findings, we propose

the possibility that Wistar-IM rats have a mutation in metal transporters, leading to a lower level of Cd in the liver and resulting in the strong resistance to the toxicity of Cd.

In conclusion, this study presents evidence that male Wistar-IM rats exhibit a strong resistance to the toxicity of Cd and this resistance is inherited as an incompletely dominant phenotype. Further studies are in progress to elucidate the mechanism of the strong resistance to the toxicity of Cd in Wistar-IM rats.

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