Effect of Low-dose 2,3,7,8-Tetrachlorodibenzo-p-dioxin on Host Resistance to Influenza Virus in Mice

Keiko Nohara 1,2, Hiroyuki Izumi 1,2, Shin-ichi Tamura 4, Ryoichi Nagata 3, Chiharu Tohyama 1,2
1Environmental Health Sciences Division, National Institute for Environmental Studies, 2CREST, JST, 3Shin Nippon Biomedical Laboratories, Ltd, 4Department of Pathology, National Institute of Infectious Diseases

Introduction: Dioxins, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most toxic congener, exert diverse biological effects in humans and animals. Host resistance, especially to virus infections, is considered one of the most sensitive targets of TCDD-toxicity, while a recent study showed that the vulnerability to TCDD of host resistance to viruses varied from experiment to experiment. Burleson et al. (Fundam. Appl. Toxicol. 29, 40, 1996) reported that a single oral dose as low as 10 ng TCDD/kg increased the mortality of mice infected with influenza A virus. If this value had been adopted as the basis for the tolerable daily intake (TDI) of dioxins, the TDI of 1-4 pg toxic equivalent (TEQ)/kg/day recommended by WHO would have to be lower. In the present study, we used the same experimental protocol described by Burleson et al. to determine whether low-dose TCDD consistently compromises the host resistance of mice infected with influenza A virus.

Materials and Methods: Four strains of mice, B6C3F1 (C57B1/6 x C3H), BALB/c, C57B1/6N and DBA/2, were purchased from Japan Charles River Inc. (Shiga, Japan). They were dosed with either corn oil or TCDD (Cambridge Isotope Laboratories, Inc., Andover, MA) by gavage at 8-weeks old. Seven days later, mice were lightly anesthetized with diethyl ether and infected intranasally with the mouse-adapted strain of influenza virus A/PR/34/8 (H1N1). After virus inoculation, mice were observed for health conditions and mortality twice a day.

Results and Discussion: In a previous study, Burleson et al. (1996) administered TCDD to female B6C3F1 mice (8 weeks old) 7 days prior to the virus infection, infected them with influenza A virus (A/Hong Kong/8/68) at doses causing 30% or fewer deaths, and found that a dose as low as 10 ng TCDD/kg increased mortality. We repeated their experiments by using the same protocol for TCDD-exposure and infection in the same strain, sex, and age of mice infected with influenza A virus (A/PR/34/8). However, a TCDD dose as high as 500 ng/kg did not increase the mortality.

We also investigated the sex- and strain-dependency of host resistance in male B6C3F1 mice and in female C57B1/6, Balb/c, and DBA/2 mice by administering the same dose range of TCDD. The results showed that TCDD doses up to 500 ng/kg did not increase the mortality of virus-infected mice in any of the strains.

Further studies on the mechanism underlying the toxicity of TCDD are needed to assess the risk of exposure to this compound in influenza A virus infection.