2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN AS A POSSIBLE ACTIVATOR OF HIV-INFECTION

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ABSTRACT

The results obtained indicate that 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) has a marked stimulatory effect on HIV-1 reproduction in primary HIV-1 infected MT-4 cell culture. Thus, there is 3-6 fold increase in the activity of reverse transcriptase in the cultures treated with 10 nM 2,3,7,8-TCDD. Besides, 4-8 fold accumulation of viral proteins were determined by immunoenzyme method.

INTRODUCTION

The development of immunodeficiency in AIDS has been associated with specific destruction of T-helper lymphocytes and with decline in their number in the peripheral blood (Popovic et al., 1984). The ratio of T4/T8 lymphocyte populations has been found to decrease under an effect of 2,3,7,8-TCDD (Hoffman et al., 1986). This agent elicits a much weaker immunodeficiency that human immunodeficiency virus (HIV) infection (Hoffman et al., 1986; Rochman et al., 1986). The mechanism of the immunotoxic action of 2,3,7,8-TCDD is still unknown. They are witnessing today a disconcerting spread of AIDS (Bourne, 1988) and concomitantly a continuous rise in the contamination of the environment with xenobiotics such as 2,3,7,8-TCDD (Poland and Knutson, 1982). The chance of the combined action of the HIV and 2,3,7,8-TCDD also appears to increase, and both actions on the target immune cells are more deleterious that each alone. Here we report the results of investigation of the effect of 2,3,7,8-TCDD upon the reproduction of the HIV in lymphoid cell culture.

METHODS

The experiments were performed with the use of a cell culture chronically infected with human immunodeficiency virus type 1 (HIV-1), this cell culture is named EVK-IRA/3, and also lymphoid cell line, namely MT-4, highly susceptible to HIV-1 infection (Schols et al., 1989). Estimates of

2,3,7,8-TCDD effects were based on determination of the activity of reverse transcriptase (Lee et al., 1987) and the amount of viral protein by the direct immunoenzyme method (Zshdanov et al., 1988).

In choice of the appropriate 2,3,7,8-TCDD concentration we took into consideration that in range of 10-150 nM 2,3,7,8-TCDD is devoid of marked cytotoxicity but it stimulates the induction of cytochrome P450IA1-containing microsomal monooxygenase system catalysing hydroxylation of benz(a)pyrene and O-deethylation of 7-ethoxyresorufin (Tsyrlov et al., 1986). The effects of 2,3,7,8-TCDD upon reproduction of the HIV in MT-4 cell culture were analysed as follows: 48 h after an application of 2,3,7,8-TCDD (time for optimal induction of microsomal cytochrome P450IA1) MT-4 cells were infected with the HIV-1.

RESULTS AND DISCUSSION

Figure 1 presents the results deal with effects of different concentrations of 2,3,7,8-TCDD on HIV-1 reproduction. There is 3-6 fold increase in the activity of reverse transriptase in the culture treated with 2,3,7,8-TCDD. Its stimulating effect was most clear-cut at 2,3,7,8-TCDD concentration of 10 nM. These data correlates well with the results of Schecter et al. (1990) who has determined a higher dioxin level in the blood samples of AIDS patients with opportunistic infections and Kaposis sarcoma in comparison with HIV-positive patients without clinical manifestation.

An increase in the activity of reverse transcriptase could not have been due to precisely its induction in the human T-cell leukemia virus type 1 used to produced MT-4 culture cells (Bohan et al., 1987) or to the induction of some other endogenous revertase because 2,3,7,8-TCDD treatment of uninfected MT-4 cell culture did not induce any revertase activity.

Concomintantly with determination of revertase activity, we studied the accumulation of viral proteins by immunoenzyme method. With the aid of ELISA we demonstrated a significant increase in viral production after the treatment of cells with 2,3,7,8-TCDD. The increase was 4-8 fold being in some dependence of 2,3,7,8-TCDD concentration applied. The results obtained indicate that 2,3,7,8-TCDD has a marked stimulatory effect upon HIV-1 production in primary HIV-infected culture. The percentage of viable cells in the 2,3,7,8-TCDD-treated culture was unaltered when compared with untreated control culture remaining as high as 60%.

Activation of HIV infection has been reported for chemical compounds, proteins and viruses (Zack et al., 1988, Nabel, 1988). The effect has been in most cases accounted for by a trans-activation of theHIV that is decisive in the regulation of its reproduction. Regulatory proteins of receptor type such as aromatic hydrocarbon (Ah) receptor, formed as a result of induction by 2,3,7,8-TCDD and able to trans-activate the cytochrome P450IA1 gene

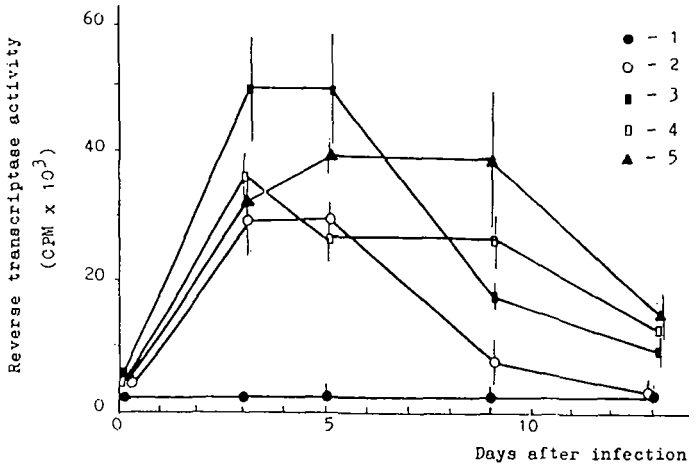

Fig. 1: Effect of various concentrations of 2,3,7,8-TCDD upon HIV-1 reproduction by the data of reverse transcriptase activity in MT-4 cells

1 - MT-4 cells incubated with 150 nM 2,3,7,8-TCDD, 2 - MT-4 cells infected by HIV-1, 3 - MT-4 cells infected by HIV-1 followed by 48 h incubation with 10 nM 2,3,7,8-TCDD, 4 - the same as that in Fig. 3 with 50 nM 2,3,7,8-TCDD, 5 - the same as that in Fig. 3 with 150 nM 2,3,7,8-TCDD.

expression (Durrin et al., 1987), may be involved in the case of 2,3,7,8-TCDD activation effect observed here. Although needing experimental verification, our assumption is that there act a similar mechanism for the activation effect of 2,3,7,8-TCDD, particularly a Ah-receptor-2,3,7,8-TCDD complex. The assumption appears the more plausible, when recalling that 2,3,7,8-TCDD being in complex with a highly specific cytosolic Ah-receptor is able to interact with the enhancer region of the human gene CYP450IA1, thereby producing a trans-activation in the construct comprising the CAT reporter gene (Jones et al., 1986).

The effect observed appears to be due to 2,3,7,8-TCDD bound to Ah-receptor because the removal of the free 2,3,7,8-TCDD does not interfere with the activation effect.

One possibility is that the effect of 2,3,7,8-TCDD may be associated with the influence of the products of an expression of a gene (or genes) on the regulatory proteins of the HIV, namely tat, art or trs, determining the level of the reproduction of the virus (Delassus and Wain-Hobson, 1988). Another possibility not to be excluded is that the activation of viral production may be the result of combined action of transcription, namely pro-

cessing, RNA stability, translation or protein stability. These and other possibilities are tested to obtain experimental confirmation with future particular reference to AIDS therapy.

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