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ROLE OF CELL CYCLE REGULATORS IN NEUTOTOXIC EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is one of the best characterized environmental pollutants and is capable of causing a wide variety of toxicities including teratogenesis. TCDD has been known to increase as well as to decrease proliferation rates depending on the experimental conditions. Toxic effects of TCDD appear to be mediated through the activation of the arylhydrocarbon receptor (AhR), a ligand-activated transcription factor, leading to induction of genes possessing the dioxin response element (DRE) in various tissues. In the present study we investigated whether TCDD inhibits neuronal proliferation in an AhR-dependent manner and whether it is mediated through alteration of cell cycle regulators using SK-N-SH human neuroblastoma cells as a model human neuronal cellular system. SK-N-SH human neuronal cells normally expressed AhR and ARNT and treatment with TCDD did not alter the message levels. TCDD-induced inhibition of proliferation in SK-N-SH cells was significantly prevented by pretreatment with a-naphthoflavone (α-NF; 5 mM), a partial AhR antagonist, or 8-methoxypsoralen (MOP; 50 mM), a binding inhibitor of activated AhR to DRE. The level of p27 was significantly enhanced by TCDD whereas expression level of p53 was not changed and consequently p21 was not induced in the TCDD-treated cells. In addition, TCDD significantly reduced phosphorylation of pRB, which was prevented by the pretreatment with α-NF or MOP. These results suggest that TCDD may induce p27 through the activation of AhR, and in turn, inhibit phosphorylation of pRB, culminating in arrested neuronal cell growth.

keyword : TCDD, Cell cycle inhibitors, Neurotoxicity