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Neurotoxic Effects of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Cerebellar Granule Cells

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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is sensitive to the central nerve system of the developing brain. It induces the cognitive disability and motor dysfunction. While TCDDD may lead to neurodevelopmental and neurobehavioral deficit, molecular mechanism and possible intracellular targets for this environmentally important chemical remain to be elucidated. Since cerebellum is responsible for certain cognitive abilities and motor function, we attempted to analyze TCDD-induced neurotoxic effects in the cerebellar granule cells. [^{3}H]PDBu binding assay indicated that TCDD induced a dose-dependent increase of total PKC activity. The induction was Ah receptor-dependent and NMDA receptor-independent. TCDD induced the translocation of both PKC-α and -ε in a dose-dependent manner. The translocation of PKC-α was AhR-dependent but that of PKC-ε was AhR-independent, indicating an isozyme-specific pattern of the induction. TCDD also induced a dose-dependent increase of the ROS formation in an AhR-dependent manner. This effect was further confirmed by the treatment of Vitamin E, an antioxidant. The treatments of cells with U0126 or MK-801 suggest that TCDD-induced ROS formation may be associated with activation of ERK-1/2 in the MAP kinase pathway or the NMDA receptor. TCDD also increased $[Ca^{2+}]_i$, which is associated with ROS formation and PKC activation in the cerebellar granule cells. It is suggested that TCDD activates the NMDA receptor, which may induce a sustained increase of $[Ca^{2+}]_i$ in neurons followed by the ROS formation. Our findings may contribute to understanding the mechanism of TCDD-related neurotoxicity, thereby improving the health risk assessment of neurotoxic compounds in humans.

Keyword: cerebellar granule cells, neurotoxicity, PKC, ROS, TCDD