

## MASTER'S THESIS

### Neurotoxicological effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on cultured neurons

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Neurotoxicological Effects of  
2,3,7,8-Tetrachlorodibenzo-*r*-dioxin  
on Cultured Neurons

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## Abstract

One major form of dioxins, namely 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), is known to be a group of highly persistent and stable compounds which is one of the major environmental pollutants that imposes serious risks to public health, such as carcinogenesis, reproductive toxicity, and neurotoxicity. N-methyl-D-aspartate (NMDA) receptors (NRs) are known to play an important role in synaptic plasticity including learning and memory. In addition, NR2B subunit is suggested to be a key molecule in the cellular memory formation, especially in the brain regions of cortex and hippocampus. In the first part of my study, the effects of TCDD on the gene and protein expressions of NR1 and NR2B subunits in cultured rat cortical and hippocampal neurons were studied. After low dose TCDD treatments (1 and 4 $\mu$ g/ml), both types of neurons were seen to survive without obvious morphological changes. The levels of NR1 and NR2B mRNAs and proteins were found to be reduced in the hippocampal neurons but NR1 and NR2B mRNAs and proteins were found to be increased in cortical neurons after TCDD treatments. The changes of NR expressions have been observed in accordance to the TCDD concentrations. In addition, results from patch-clamp recording also showed that NMDA-induced peak inward currents were also reduced in the hippocampal neurons after 20 $\mu$ g/ml TCDD treatments. These results indicate that TCDD down-regulates the expression of NR1 and NR2B subunits and may cause deficits in NMDA receptor functions. These may impose a serious threat in formation of cellular memory in the hippocampal neurons.

Moreover, in the second part of my study, the effects of TCDD on the protein expression of tyrosine hydroxylase (TH; a synthetic enzyme for the neurotransmitter dopamine) in cultured dopaminergic neurons of the rat substantia nigra were investigated. After low doses of TCDD treatments (0.1, 1 and 4 $\mu$ g/ml), TH-positive neurons were also seen to survive with no obvious morphological changes. Western blot experiments and immunofluorescence showed that TH immunoreactivity and proteins were found to be reduced in the nigral neurons after TCDD treatments. The reduction is also found to be dose dependent. These results indicate that TCDD may cause deficits in dopamine neurotransmission in the dopaminergic neurons and may contribute in the onset of Parkinson's disease in humans.

In conclusion, results of the present study have provided important pieces of evidence that low doses of TCDD in  $\mu$ M range (lower than the acceptable level of dioxin) are neurotoxic and may cause deficits in functions of the nervous system.

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