Karolinska Institutet

Institutionen för Neurovetenskap

Assessment of environmental contaminants' neurotoxicity : in vitro and in vivo experimental studies

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SUMMARY

Accumulating evidence points to environmental contaminants as possible causes of neuronal damage in developing organisms. A prerequisite to prevention is the recognition of a chemical's harmful effects during development. The knowledge that an environmental contaminant is neurotoxic can prompt efforts to restrict its use and to limit the exposure. Many studies on environmental toxicants have been performed so far, but the knowledge available on the effects of exposures at low, environmentally relevant doses, and on cell-specific mechanisms of action is still limited. The work included in this thesis is based on an experimental strategy including *in vitro* studies and behavioral analyses aimed at investigating the potential neurotoxic effects of selected food contaminants, such as polychlorinated biphenyls (PCBs), methylmercury (MeHg) and perfluorinated chemicals (PFCs). Using *in vitro* models, we found that MeHg and PCBs cause cell death in the hippocampal cell line HT22 via a parallel activation of calpains and lysosomal proteases, with no involvement of caspases. Oxidative stress does not play a major role in PCBs toxicity, opposite to MeHg and co-exposure to PCBs and MeHg show mostly antagonistic interactions. We have also investigated the effects of non-dioxin like (NDL)-PCBs 153 and 180 and MeHg on primary cultures of rat neural stem cells (NSCs). Both PCBs promote neuronal differentiation and decrease NSCs' proliferation by repressing Notch signaling. Conversely, exposure to MeHg inhibits neuronal differentiation and promotes the proliferation of NSCs by stimulating Notch signaling. The effects on differentiation were confirmed by the changes in the number of cells showing spontaneous Ca^{2+} activity following the exposure to PCBs or MeHg. Combined exposures to PCBs and MeHg resulted in antagonistic effects on spontaneous neuronal differentiation, but induced apoptosis, which was not observed with single exposure to either chemical. We used the same model for investigating the effects of nanomolar concentrations of perfluorooctane sulfonate (PFOS), and we found that PFOS stimulates neuronal and oligodendrocytic differentiation in a dose-dependent manner by upregulating PPARγ and the downstream gene, mitochondrial uncoupling protein 2 (UCP2). Importantly, the effects were confirmed in mouse neonatal brains after prenatal exposure to PFOS, where we found an increased expression of PPARγ and the downstream gene UCP3. We then investigated the effects of PFCs *in vivo* by assessing the behavioral alterations induced by *in utero* exposure to PFOS or perfluorooctanoic acid (PFOA). We investigated the motor function, circadian activity, and emotion-related behavior. Exposure to PFOS results in decreased locomotion in a novel environment and reduced muscle strength only in male offspring. Prenatal exposure to PFOA is associated with changes in exploratory behavior in both male and female offspring, and increased home cage global activity only in males. In conclusion, our studies show that even very low doses (in the nanomolar range) of selected food contaminants, and the effects found *in vitro* are consistent with the results from *in vivo* exposure. Therefore, a combined approach with both *in vitro* and *in vivo* experimental models is most valuable for developmental neurotoxicity testing.

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