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## Converging effects of a PCB mixture, bisphenol A and chlorpyrifos on the expression of genes regulating neural progenitor identity, interneuron development and gliogenesis in developing rat hippocampus

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Developmental exposure to polychlorinated biphenyls (PCBs), bisphenol A (BPA) or the pesticide chlorpyrifos (CPF) impairs hippocampus-dependent behaviors (learning) in adult offspring. In a search for shared effects on gene networks, we treated pregnant rats with PCB mixture Aroclor1254 (5, 0.5 mg/kg), BPA (5, 0.5 mg/kg), or CPF (3, 1 mg/kg) in the feed (PCB, BPA) or subcutaneously (CPF). Transcriptome analysis was done in hippocampus from offspring at postnatal day six (PND6) by NGS. In male hippocampus, analyses revealed common effects on genes regulating hippocampal development. At behaviorally active doses, all chemicals showed upregulation of *Gli3*, *neuregulin1*, *ErbB4*, *Sox6*, *Sox11*, *Pou2f2/Oct2*, *Pou3f2/Brn2* and *Wnt* receptors *Fzd3* and *Fzd6*. *microRNA-24* was down-regulated, indicating possible interactions with post-transcriptional regulation of *Sox6*. *Pou2f1/Oct1*, *Pou3f3/Brn1*, *Sox2* and *Sox17* was affected by only two treatments. Effects on *Sox6*, *Nrg1*, *ErbB4*, *Oct1* were confirmed by real time RT PCR. Analyses of proteins and female hippocampus are in progress. Involvement of *Nrg1*, its receptor *ErbB4* and *Sox6* suggests effects on interneuron development. In postmitotic interneurons of PND6, *Sox6* controlled interneuron subtype diversity. Expression changes were observed in interneuron-related genes. The increase of *Sox6* mRNA levels relative to mRNA levels of *Sox5*, its counterpart in postmitotic corticofugal projection neurons also suggests a specific effect in interneurons. *Sox6* further controls gliogenesis in hippocampus; *Sox6* overexpression represses specification and terminal differentiation of oligodendrocyte precursors. In conclusion, our investigation revealed convergent actions of different types of behaviorally active chemicals on genes involved in the control of major developmental processes in hippocampus.

### Biography

Walter Lichtensteiger has served as a Professor of Pharmacology and Toxicology at the University of Zurich, Switzerland, with teaching obligations at the Swiss Federal Institute of Technology (ETH), Zurich and after retirement, he founded the spin-off company GREEN Tox (Group for Reproductive, Endocrine and Environmental Toxicology) in 2005, together with Margret Schlumpf. GREEN Tox focuses on "Research and continuous education on environmental chemicals". He is a member of several committees of the OECD programme for testing of chemicals.

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