



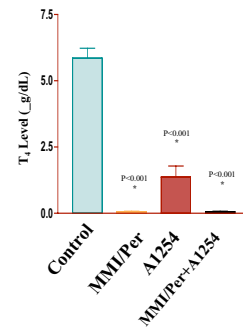
Maternal PCB Exposure Alters Thyroid Hormone Mediated Oligodendrocyte Development

OVERVIEW

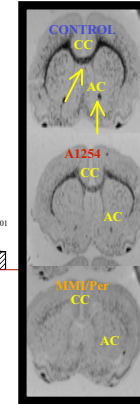
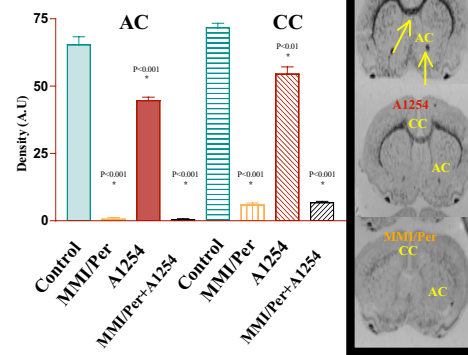
The objective of this research project is to understand the mechanism by which maternal exposure to polychlorinated biphenyls (PCBs) can have a toxic effect on the development of oligodendrocytes in the neonatal rat brain. It is well accepted that thyroid hormone (TH) acts on oligodendrocyte precursor cells and mature oligodendrocytes by directing survival, differentiation, and myelination. Moreover, these developmental processes have been shown to be mediated by specific thyroid hormone receptor (TR) isoforms. Therefore, the goal of this project is to determine how TH and TRs mediate the toxic effect of PCBs on oligodendrocyte development. The initial findings on the effects of PCB-induced hypothyroxinemia altering oligodendrocyte development are presented here.

RESEARCH HIGHLIGHTS

Developmental Exposure to PCBs Reduce Circulating Levels of Thyroid Hormone



Developmental Exposure to PCBs Reduce MAG-mRNA in the AC/CC



METHODS

- Timed pregnant rats were dosed with Aroclor1254 (5mg/kg/day), Methimazole/Perchlorate (to induce experimental hypothyroidism), or a combination MMU/Per+A1254 from gestational day-6 (G6) to postnatal day-15 (P15)
- Radioimmunoassay was used to determine circulating T₄ levels on P15
- *In situ* hybridization using a myelin-associated glycoprotein (MAG) probe was used to label oligodendrocytes on P15 tissue sections.
- Cell numbers, oligodendrocyte numbers, and single cell MAG-mRNA levels were determined in the anterior commissure (AC) and corpus callosum (CC).

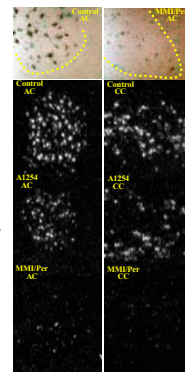
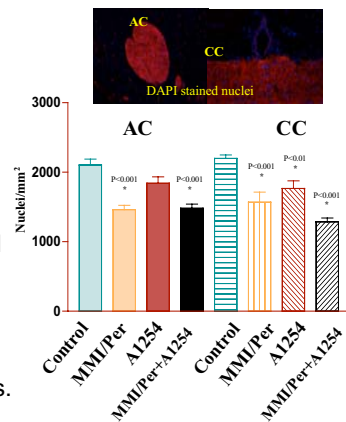
CONCLUSION

- These studies show that PCBs have an effect similar to methimazole on serum T₄ levels
- Furthermore, PCBs affect the total number of cells and the number of oligodendrocytes in the AC/CC in a manner consistent with the effects of methimazole
- However, cellular levels of MAG mRNA indicate that the effects of PCBs on TH-mediated oligodendrocyte development may not be solely due to lower serum T₄.

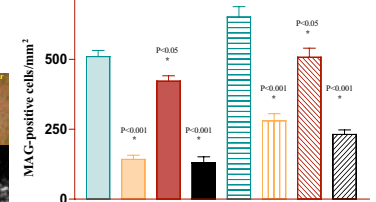
RESEARCH IMPORTANCE

- Thyroid hormone is essential for normal brain development. Therefore, any environmental chemical that may alter TH homeostasis has the potential to alter brain development. In fact, neurological deficits reported to be associated with maternal and fetal thyroid dysfunction- lower IQ scores, reduced visual recognition memory, and motor deficits, among others- are similar to deficits associated with developmental PCB exposure. Moreover, concentrations of PCBs in maternal and chord blood are often associated with lower TH levels and consistently decrease circulating levels of TH in experimental animals.
- Not all observations are consistent with the hypothesis that PCBs produce adverse effects by reducing TH levels. Reports have demonstrated TH-like effects of PCBs on TH-responsive genes despite a measured reduction in circulating TH.

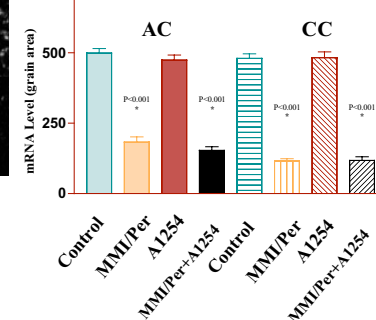
PCBs Reduce Cells Numbers in the AC/CC



PCBs Reduce Oligodendrocyte Numbers in the AC/CC



PCBs do not effect cellular levels of MAG-mRNA



FUTURE DIRECTIONS

- Future research will be aimed at:
- Determining whether the effects of PCBs on oligodendrocyte development is due to TH levels or effects at the TR
 - The ability of T₄ to restore cell numbers in PCB exposed animals will be tested
 - Investigate the necessity of TRs in the PCB induced alteration of oligodendrocyte development using the precursor cell line CG-4 and cells derived from TR-knockout mice

ACKNOWLEDGEMENTS

R. Thomas Zoeller- Thesis Advisor