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aternal PCB Exposure Alters Thyroid Hormone Mediated Oligodendrocyte Development

OVERVIEW

objective of this research project is to understand the hanism by which maternal exposure to polychlorinated enyls (PCBs) can have a toxic effect on the development igodendrocytes in the neonatal rat brain. It is well epted that thyroid hormone (TH) acts on oligodendrocyte ursor cells and mature oligodendrocytes by directing ival, differentiation, and myelination. Moreover, these elopmental processes have been shown to be mediated pecific thyroid hormone receptor (TR) isoforms. refore, the goal of this project is to determine how TH and mediate the toxic effect of PCBs on oligodendrocyte elopment. The initial findings on the effects of PCB- ced hypothyroxinemia altering oligodendrocyte elopment are presented here.

RESEARCH IMPORTANCE

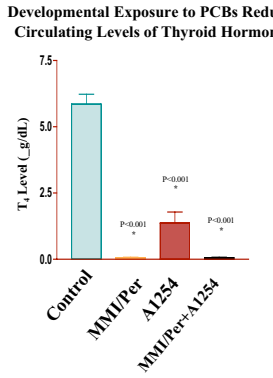
yroid hormone is essential for normal brain elopment. Therefore, any environmental chemical may alter TH homeostasis has the potential to alter n development. In fact, neurological deficits reported e associated with maternal and fetal thyroid unction- lower IQ scores, reduced visual recognition mory, and motor deficits, among others- are similar to cits associated with developmental PCB exposure. eover, concentrations of PCBs in maternal and chord od are often associated with lower TH levels and sistently decrease circulating levels of TH in erimental animals.

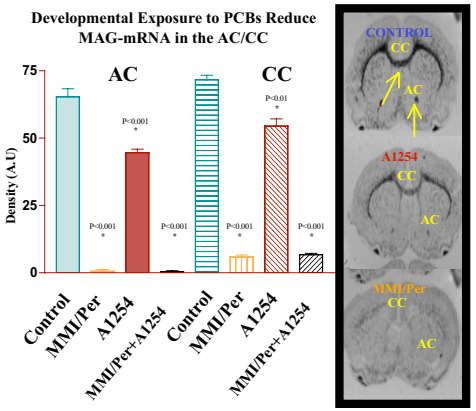
ot all observations are consistent with the hypothesis PCBs produce adverse effects by reducing TH levels. orts have demonstrated TH-like effects of PCBs on responsive genes despite a measured reduction in ulating TH.

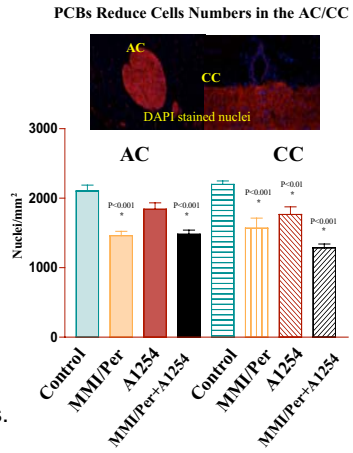
ACKNLOWDGEMENTS

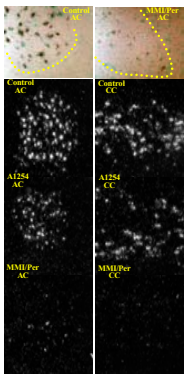
R. Thomas Zoeller- Thesis Advisor

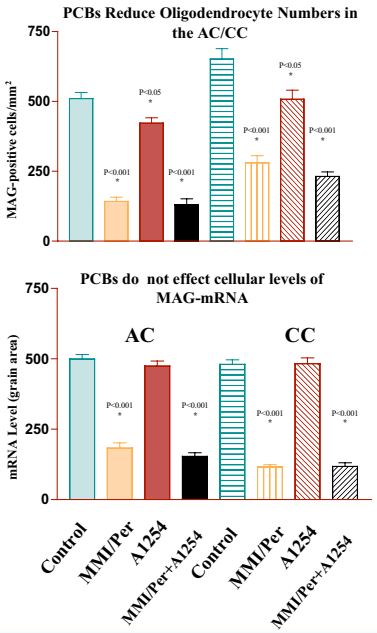
RESEARCH HIGHLIGHTS











METHODS

- Timed pregnant rats were dosed with Aroclor1254 (5mg/kg/day), Methimizole/Perchloarte (to induce experimental hypothyroidism), or a combination MMI/Per+A1254 from gestational day-6 (G6) to postnatal day-15 (P15)
- Radioimmunoassay was used to determine circulating T_4 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 determine in the anterior commissure (AC) and corpus collosum (CC).

CONCLUSION

- These studies show that PCBs have an effect similar to methimizole on serum T_4 levels
- Furthermore, PCBs affect the total number of cells and the number of oligodendrocytes in the AC/CC in manner consistent with the effects of methimizole
- 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 T_4.

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 T_4 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

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