Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroxine and TSH blood levels in rats and mice

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I. Introduction

Many studies have shown that persistent chlorinated aromatics could affect thyroid hormone homeostasis. One group of these environmental pollutants, the polychlorinated biphenyls (PCBs), have in several experimental studies given rise to altered blood thyroxine levels [1, 2]. PCB exposure during pregnancy has resulted in thyroid hormone alterations in mouse fetuses [3] and in neonatal rat offspring [4, 5]. Also, epidemiological studies indicate an alteration in thyroid hormone homeostasis in children that is correlated with gestational exposure to PCBs and dioxins [6]. Interestingly, earlier indicated PCB effects on the developing CNS, observed as e.g. cognitive and motor deficits [7], could have a reasonable explanation, as early thyroid hormone alterations could affect CNS development leading to irreversible damages [8]. The mechanism behind the thyroid hormone alterations by PCB is not clearified, but could include binding to the thyroxine plasma transporter transthyretin (TTR) [9], induction of enzymatic conjugation and exretion of thyroxine [10], or direct effects on the thyroid gland [11].

In this study we report on effects of halogenated aromatics on rats and mice. In contrast to PCBs, where earlier data is present, the brominated flame retardant group have been very little studied. Therefore, we have followed thyroxine (and TSH) levels in animals exposed to technical grade or pure congener polychlorinated diphenyl ethers (PBDEs), using PCBs for comparative purposes. This study will try to answer the following questions: How potent, in terms of thyroid hormone effects, are PBDEs compared to PCBs?; Are the observed efffects dose-related?; Are the choosen pure PBDE and PCB congeners more or less potent than the technical grade preparations?; Are there differences in sensitivity between rats and mice?

2. Methods

Female rats (S-D) and mice (C57BL), both species 7 week old (approx. wt. 175 and 20 g, respectively) were administered daily oral doses, dissolved in oil, of the following compounds (rats only the technical grade substances) over a 14 days period: Bromkal 70 (a technical grade PBDE containing approx. 40% TBDE), 2,2',4,4'-tetrabromodiphenyl ether (TBDE), Aroclor 1254 (a technical grade PCB containing approx. 5% PeCB), or 2,3,3',4,4'-pentachlorobiphenyl (PeCB; a mono-ortho PCB with certain Ah-receptor affinity). The technical grade preparations were gifts from other labs, whereas the pure congeners were synthesized by Dr. Åke Bergman and coworkers, Environmental Chemistry, Stockholm University.

Treatments, daily doses and group sizes were as given in the following table:

treat	contr	PBDE			PCB	
		Bromkal 70		TBDE	Aroclo	PeCB
dose	-	18mg/	36 mg/	18 mg/	10 mg/	10 mg/
rats	10	6	6	-	6	-
mice	12	8	8	8	8	8

The total dose (given over the whole 14 day-period) was for the PBDE animals 250 and 500 mg/kg body wt., respectively, and for the PCB animals 140 mg/kg. The animals receiving the low PBDE dose were calculated to receive the same molar dose as the PCB animals.

The animals were killed 24 hr after the last PBDE/PCB administration, and blood was collected. The blood was centrifuged and the plasma was taken for thyroxine and (rats only) TSH measurements by use of commercial kits (total T4: Amerlex M, Johnson Diagnostics; TSH: rTSH(^{125}I) assay system, Amersham).

3. Results and discussion

The thyroxine and TSH data on rats and mice are given in tables 1 and 2 (mean values ±S.D.). Values within brackets are the percentage values of the controls.

Table 1: Thyroxine and TSH levels in PBDE/PCB-treated rats

treatment	thyroxine (nmol TT4/l)	TSH (ng/tube)
control	33 ±7	0.48 ±0.17
Bromkal, low dose	20 ±10 (61%)	0.46 ±0.12 (96%)
Bromkal, high dose	17 ±3 (52%)	0.44 ±0.12 (92%)
Aroclor 1254	13 ±1 (38%)	0.66 ±0.15 (138%)

Table 2: Thyroxine levels in PBDE/PCB-treated mice

treatment	thyroxine (nmol TT4/l)
control	63 ±9
Bromkal, low dose	53 ±8 (84%)
Bromkal, high dose	40 ±9 (63%)
TBDE	44 ±5 (69%)
Aroclor 1254	34 ±6 (54%)
PeCB	28 ±4 (44%)

The results show that PBDE decreased the total thyroxine levels both in rats and mice, and a dose-related effect was indicated at the investigated Bromkal doses. Effects of a technical grade PBDE mixture on thyroid hormone levels have earlier been shown by Fowles and coworker [12]. Their results from the subcronic study are similar to what we obtain; their reported non-dose-related effects on thyroxine levels after low single doses of PBDE is however questionable. In this paper the PBDE effects on thyroxine, as compared to PCB, seem of lower potency. Results from the TSH measurements in rats showed that these levels were generally not affected. In the Aroclor group, a certain increase in levels was however noted.

If one compare the pure congeners against the technical mixtures (in mice only) the pure congener seem to be more effective in thyroxine-lowering aspect. This is of course depending on what kind of congeners what are tested; in the case of PeCB it has earlier been show that PeCB metabolites, and certain other PCB metabolites, have high affinity for the thyroxine transport protein in blood, transthyretin (TTR) [13].
Lastly, comparing rats and mice as regards thyroid hormone effect seems to suggest that the rat is the more sensitive species.

4. Conclusion

To conclude, it has been shown that both PBDE and PCB are able to lower thyroxine levels in plasma of rats and mice, which in case of PBDE has been studied very little before. However, PCB seemed more potent i our model. Generally, TSH does not seem to be a good indicator of halogenated aromatic exposure. The rat seemed more sensitive in our thyroxine model than the mouse, and the pure congeners we had choosed seemed more effective than technical mixtures. The presented results may be of use in the ongoing search for (a) mechanism(s) behind the effect of these chemicals on the developing CNS.

5. References

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