Structure-dependent multiple interactions of polyhalogenated aromatic hydrocarbons with the thyroid hormone system

Abraham Brouwer

Division of Toxicology, Department of Food Technology & Nutritional Sciences, Agricultural University Wageningen, P.O. Box 8000, 6700 EA Wageningen, The Netherlands

Introduction

The possible presence of chemical compounds exhibiting endocrine modulating effects in our food and in the environment has attracted much attention of researchers, policy makers and the public opinion over the last 5 years. While the major focus has been on putative pseudo-estrogenic compounds, there is also ample evidence for interactions of natural and man-made chemicals with other hormonal systems, such as the thyroid hormone system .In this paper an overview is given on the structure-dependency, and the multiplicity of the interactions of polyhalogenated aromatic hydrocarbons (PHAHs) with the thyroid hormone system (1).

Effects on circulating thyroid hormone levels

Many reports have indicated that exposure to PHAHs, either as single congeners, or as mixtures did result in severe reductions of plasma total and free thyroxine (TT_4 and FT_4) levels, while only little effects were found on plasma total triiodothyronine (TT_3) concentrations in various rodent species, and in primates (1). Polychlorodibenzo-p-dioxins (PCDDs), -dibenzofurans (PCDFs) as well as dioxin-like non-ortho and mono-ortho PCB congeners were found to reduce thyroxine levels in plasma with relative potencies that followed their respective TEF values quite closely (2). However, the magnitude of plasma T_4 reductions induced was much larger for PCB congeners that are fairly easy metabolised, such as 3,3',4,4'-TeCB (PCB 77), 2,3,3',4,4'-PeCB (PCB 105) and 2,3',4,4',5-PeCB (PCB 118). In addition, the di-ortho PCB, 2,2',4,4',5,5'-HxCB was found to reduce plasma T_4 levels, as well albeit at much higher concentrations, indicating that T_4 reductions may be mediated by, but are not exclusively linked with the Ah receptor pathway.. Several other classes of PHAHs have also been found to reduce T_4 levels in rodents (1), such as hexachlorobenzene (HCB), pentachlorophenol (PCP) and other chlorinated phenols, tetrachlorobenzyltoluenes (TCBTs), chlorinated and brominated diphenylethers (TCDEs and TBDEs). Reductions in T_4 levels were also observed in rodent fetuses and neonates, following exposure of the dams to PHAHs

(3-5). Moreover, PHAH exposure has also been found to be associated with lower plasma thyroxine levels in seals (6,7), in fish-eating birds (8,9) as well as in human infants (10,11)

Multiple interactions with thyroid hormone metabolism

Many studies have been performed to elucidate the mechanism(s) involved in the thyroid hormone reductions by PHAHs. Overall, three levels of interference in the thyroid system have been found for PHAHs, including the thyroid gland, thyroid hormone metabolism and thyroid hormone transport (1). In addition, there are some reports indicating a poor thyroid stimulation hormone (TSH) feedback response despite severe plasma T4 reductions induced, which suggests that a fourth level of interference may exist involving the pituitary-thyroid axis (4,12).

Most, if not all, enzyme systems involved in thyroid hormone metabolism have been found to be affected by PHAHs. This includes the UDP-glucuronyl transferases (UGTs), the deiodinases (IDs), and the sulfotransferases (SULTs). At least two out of three of the UGT isozymes involved in thyroid hormone glucuronidation were found to be induced in the liver of rats upon exposure to PHAHs (2). The phenol-UGT, or UGT1A1 isozyme, is highly induced by dioxin-like PHAHs, through an Ah-receptor mediated mechanism. Non-dioxin like PCBs, such as 2,2',4,4',5,5'-HxCB (PCB 153) and mixed inducers, such as 2,3,3',4,4',5-HxCB (PCB 156) also induce T4 glucuronidation, however through induction of another isozyme, the UGT1A2 isozyme.(2). In both cases, the induction of the UGT-isozymes is most likely caused by the parent PHAHs.

With respect to the iodothyronine deiodinases (IDs), there is a more complex interaction of PHAHs. Studies have revealed a competitive inhibition of ID activity, mainly isozyme ID-1, by hydroxylated metabolites of PHAHs, but not their parent compounds (13). However, the isozyme ID-II, which is involved in the bioactivation of T4 to T3 in brain and other target tissues of thyroid hormones, was found to be increased in activity in fetal brain, following exposure of the dams during gestation to PHAHs (4). The increase of ID-II activity is not caused by a direct effect of PHAHs, but most likely occurred as a consequence of thyroxine reductions induced by PHAHs in the fetal brain and may be considered as a compensatory mechanism to low T4 levels in order to maintain the level of active T3 in the fetal brain. The sulfotransferases (SULTs) are also affected by PHAHs, but this will be dealt with in detail in the paper of Schuur et al.(14).

Structure-dependent interactions with thyroid hormone transport

Interactions of PHAHs with the plasma transport of thyroxine has been observed both in vitro and in vivo in rodents and in marmoset monkeys (1). Hydroxylated metabolites of PHAHs were found to be potent, competitive inhibitors of T_4 binding to transthyretin (TTR), the major thyroid hormone transporter in most species. In vivo, interaction of hydroxylated PHAHs with TTR results in dramatic reductions in plasma T_4, but also in plasma retinol-RBP which is normally bound to TTR and disrupted by the hydroxy-PHAH as well (15). The structural requirements for TTR binding have been and are being studied in great detail, using

both in vitro competitive binding studies, graphics-assisted computer modelling and X-ray diffraction of TTR-hydroxy-PHAH co-crystals (16). Structural requirements involve, a hydroxyl group on the meta, or para position of an aromatic ring, with one, or more adjacent halogens substituted on the phenolic ring (16). Planarity of the molecule is not a requirement for binding. In fact, chlorinated phenols, like PCP, bind equally well to TTR as hydroxy-PCBs, -PCDDs, -PCDFs or -PCDEs. The highest relative potencies for binding to TTR are observed for the brominated PHAHs, tetrabromo-bisphenol A (TBrBPA: 25-fold more potent than T_4), and pentabromophenol (PBrP: about 20-fold more potent that T_4). The most potent chlorinated phenolic compounds are 5 to 8 times more potent than T_4, such as 4-OH-2,3,3',4',5-PeCB (metabolite of PCBs 105 and 118), PCP and the 4,4' (OH)2-3,3'5,5'-TeCB. The other phenolic PHAHs have potencies ranging from equal to T_4 to several orders of magnitude less than T_4. X-ray diffraction has revealed that several of the phenolic PHAHs bind in a forward mode (hydroxy-group first in) in the central channel of the TTR molecule (16).However, recently a novel, reverse mode (hydroxy-group last in) of binding was discovered for pentabromophenol as well as TBrBPA (Ghosh, personal communication).

Role of TTR in fetal transport of hydroxy-PHAHs

Binding to TTR not only disrupts the T_4 transport, with concomitant low plasma T_4 levels, but may also result in the selective transport of the hydroxylated PHAH across the blood-brain barrier and the placental barrier. TTR has been suggested to play a major role in mediating the delivery of T_4 from the mother to the fetus across the placental barrier, but also across the blood-brain barrier, where T_4 is locally converted to T_3,which is absolutely essential for e.g., brain development (17,18).

In experiments where pregnant rats were exposed to ^{14}C-3,3',4,4'-TeCB, large quantities of radiolabel were found to accumulate in the fetal compartment at the end of gestation. Accumulation of label was particularly high in fetal brain, and was found to be mainly the hydroxylated metabolite, 4-OH-3,3',4',5-TeCB (19). High fetal accumulation of the hydroxy-metabolite 4-OH-2,3,3',4',5-PeCB was found following exposure of the dams to Aroclor 1254 from day 10 to 16 of gestation (4). Recently Meerts (personal communication) also found very high accumulation of radiolabel in fetal brain, following maternal exposure to the hydroxy-metabolites 4-OH-2,3,3',4',5-PeCB, or TBrBPA. These results strongly suggest that TTR facilitates the efficient transfer over blood-brain and placental barrier's of phenolic PHAHs in particular. The possible impact of the high accumulation of phenolic PHAHs on the development of fetal brain , behaviour and reproductive organs and functions is the focus of ongoing investigations.

Acknowledgements

The author wishes to thank all the investigators of the various laboratories that have contributed to the studies presented in this overview. Part of the data presented were derived from the so- called RENCO project, sponsored by the European Commission, Environment and Climate Programme. (coordinator Prof. Åke Bergman, Wallenberg Laboratory, Stockholm University Sweden)

References

1. Brouwer, A., Morse, D.C., Lans, M.C., Schuur, A.G., Murk, A.J., Klason-Wehler, E., Bergman, A. And Visser, T.J; Toxicol. & Industr. Health. **1998**, 14(1/2), 59.
2. Van Brigelen, A.P.J.M., Smit, E.A., Kampen, I.M., Groeneveld, C.N., Fase, K.M., Van der Kolk, J., Poiger, H., Van den Berg, M., Koeman, J.H. and Brouwer, A.; Eur. J. Pharmacol.[Environm. Toxicol. & Pharmacol. Section] **1995**, 293, 77.
3. Ness, D.K., Schantz, S.L., Moshtaghian, J. and Hansen, L.G.; Toxicol. Lett. **1993**, 66, 311.
4. Morse, D.C., Klasson-Wehler, E., Wesseling, W., Koeman, J.H. and Brouwer, A.; Toxicol. Appl. Pharmacol. **1996**, 136, 269.
5. Darnerud, P.O., Morse, D.C., Klasson-Wehler, E. And Brouwer, A.; Toxicol. **1996**, 106, 105.
6. Brouwer, A., Reijnders, P.J.H. and Koeman, J.H.; Aquat. Toxicol. **1989**, 15, 99.
7. Ross, P.S. (Thesis), Seals, pollution and disease: Environmental contaminant-induced immunosuppression, Utrecht University, **1995**, ISBN 90-393-0780-6.
8. Van den Berg, M., Craane, B.L.H.J., Sinnige, T., Van Mourik, S., Dirksen, S., Boudewijn, T., Van den Gaag, M., Lutke-Schipholt, I.J., Spenkelink, A. And Brouwer, A.; Environm. Toxicol. Chem. **1994**, 13(5), 803.
9. Murk, A.J., Bosveld, A.T.C., Van den Berg, M. and Brouwer, A.; Aquatic Toxicol. **1994**, 30, 91.
10. Koopman-Esseboom, C., Morse, D.C., Weisglas-Kuperus, N., Lutke-Schipholt, I.J., Van der Paauw, C.G., Tuinstra, L.G.M.T., Brouwer, A. and Sauer, P.J.J.; Pediatr. Res. **1994**, 36(4), 468.
11. Nagayama, J., Iida, T., Hirakawa, H., Matsueda, T., Tsuji, H., Okamura, K., Hasegawa, M., Sato, K., Kitahara, E., Ma, H.-Y., Yanagawa, T., Igarashi, H., Fukushige, J.I. and Watanabe, T.; Organohalog. Comp. **1996**, 30, 228.
12. Barter, R.A. and Klaassen, C.D.; Toxicol. Appl. Pharmacol. **1994**, 128, 9.
13. Adams, C., Lans, M.C., Klasson-Wehler, E., Van Engelen, J.G.M., Visser, T.J. and Brouwer, A.; Organohalog. Comp. **1990**, 1, 51.
14. Schuur, A.G., Tacken, P.J., Visser, T.J. and Brouwer, A.; Environm. Toxicol. & Phanrmacol. **1998**, 5, 7.
15. Brouwer, A. and Van den Berg, K.J.; Toxicol. Appl. Pharmacol. **1986**, 85, 301.
16. Lans, M.C. (Thesis), Thyroid hormone binding proteins as novel targets for hydroxylated polyhalogenated aromatic hydrocarbons (PHAHs): possible implications for toxicity, Wageningen Agricultural University, **1995**, ISBN 90-5485-430-8.
17. Calvo, R., Obregon, M.J., Ruiz de Ona, C., Escobar del Rey, F. And Morreale de Escobar, G.; J. Clin. Invest. **1990**, 86, 889.
18. Southwell, B.R., Duan, W., Alcorn, D., Brack, C., Richardson, S.J., Kohrle, J. And Schreiber, G.; Endocrinol. **1993**, 133(5), 2116.
19. Morse, D.C., Klasson-Wehler, E., Van de Pas, M., De Bie, A.T.H.J., Van Bladeren, P.J. and Brouwer, A.; Chem. Biol. Interact. **1995**, 95, 41.