DISRUPTION OF THYROID HORMONE STATUS BY PERSISTENT AND LABILE ORGANIC POLLUTANTS (POPS AND LOPS).

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Introduction

Thyroxine (T4) and triiodothyronine (T3) are the main products of the thyroid gland in vertebrates. Peripherally, T4 can be converted by 5'-deiodinase (outer ring) to the active T3 or to the inactive reverse T3 by 5-deiodinase (inner ring). About 60% of extra-thyroidal T4 is in the liver where excess T4 can be conjugated by UDP glucuronosyl transferases (UDPGTs) and T3 can be conjugated by phenol sulfotransferases facilitating biliary excretion [1, 2]. Add to this the synthetic pathways and iodine scavenging from degradation products and the system is vulnerable to perturbations by a number of dietary, pharmacologic and xenobiotic agents which affect gene expression, enzyme activities, and energy status [1, 2, 3, 4].

Moreover, the primary status of thyroid hormones is controlled by the hypothalamo-pituitary-thyroid (HPT) axis and the hypothalamus and pituitary are also subject to perturbations. T3 and, to a lesser extent, other thyroid hormones control a number of gene expressions and energy metabolism themselves; thus, nearly every system in a vertebrate animal may be perturbed by changes in thyroid hormone status. The potential for harm is great, especially during critical windows of development. Due to multiple and interactive mechanisms of interference, practically any toxicant may have a direct or indirect effect on thyroid hormone status at some dose. Yet, health effects unambiguously attributed to even halogenated aromatic-induced changes in thyroid hormone status are not as common as the above relationships would predict [5].

Are we overstating the importance of thyroid hormones? Are the toxicants ineffective and non-additive at environmental and food chain exposure levels? Are the number of unknowns [5, 6] too great to make the critical connections? Or, are we too caught up in the discoveries of the moment to make the connections?

Methods

Comparisons will be made of several factors which influence outcomes in order to catalog part of what is known. This may illustrate that we really know more about four facets of thyroid hormone economy than we are using. The four major points of vulnerability considered will be:

1) Thyroid gland structure and function;
2) Regulation of the thyroid gland through the HPT axis;
3) Thyroid hormone metabolism; and
4) Thyroid hormone transport, including serum binding proteins and hepatic uptake.

In addition to stress factors and diurnal variation, selection of gender, age, dosing regimen, endpoints and model toxicants may greatly influence the outcomes [7]. Special attention will be paid to study designs because the fact that different designs yield different comparative results does not

necessarily mean one of the studies is wrong. These differences actually provide valuable information.

Results and Discussion

Both persistent and metabolically labile (non-persistent) halogenated aromatic compounds have been shown to disrupt various aspects of the hypothalamo-pituitary-thyroid axis and disturb thyroid economy. Aryl hydrocarbon receptor (AhR) agonists have been the most studied; these include polychlorinated dibenzo-*p*-dioxins (PCDDs) such as 2,3,7,8-tetraCDD, polychlorinated dibenzofurans (PCDFs), coplanar polychlorinated biphenyls (PCBs) such as 34-34 tetraCB (CB 77) and 345-34-pentaCB (CB 126), and mono-*ortho* PCBs such as 245-34-pentaCB (CB 118) and 2345-34-hexaCB (CB 156). TCDD is the most potent in reducing serum T4, but the labile CB 77 and mono-*ortho* CB 118 are more efficacious [8, 9]. The major mechanism for AhR-mediated disruption of thyroid economy has been shown repeatedly to be induction of UDPGTs and biliary excretion of the conjugate. CB 77 acts through the same mechanism, although at higher doses; at least a metabolite of CB 77 displaces T4 from the main carrier protein in rats, prealbumen, making it more vulnerable to the enhanced phase 2 metabolism [1].

Thyroid status can also be reduced, however, by very weak UDPGT inducers such as CB 95 (236-25) [10, 11, 12] or vapor phase PCBs collected over a Superfund electrical landfill [13]. In short-term protocols with non-persistent PCBs (e.g 72 hr between first dose and sample collection), UDPGTs are not maximally induced but serum T4 has reached maximal depletion[11, 14]; in many cases, delay of sampling to 96 hr may result in some recovery of thyroid status [7]. These brief declines may only be biologically significant if they occur during a critical window of developmental vulnerability.

The limited efficacy of induced T4 metabolism was directly measured in a study of UDPGT activity and excretion of T4-glucuronide by male rats. AhR agonists (TCDD, high TEQ type A Aroclor 1254, CB 126 and CB 118) induced UDPGT and increased biliary excretion of T4-glucuronide (Martin 2002). Aroclor 1242 is a weaker AhR agonist and had a lower effect on UDPGT and biliary excretion; CB 99 (245-24-pentaCB) is a strong phenobarbital-type (PB) inducer while CB 95 is a very weak PB inducer; neither congener increased biliary excretion of T4-glucuronide even though they both caused significant decreases in serum T4 and T3 [12].

All eight mixtures/chemicals, except CB 95, increased relative liver weights following the single dose which suggested that part of the serum T4 depletion may be partly due to hepatic uptake. Seven day pretreatment with Aroclors 1254 (type A) and 1242 increased the hepatic uptake of radiolabeled T4 within 1 minute following injection and sustained the increased liver content for the entire 30 minute duration of monitoring [12].

In the 7-day dosing regimen above with male rats, the persistent inducer, CB 99, was more potent and efficacious than the labile CB 95. In female rats using a 2-day dosing regimen, the opposite relationship between the two congeners was observed [7].

Aroclor 1254 has been reported to suppress the thyroid response to TSH [2]. Recent studies have shown that CB 95 and, to a lesser extent, the slightly more persistent and stronger inducer CB 101 (245-25-pentaCB) suppress the pituitary response to TRH [10]. This effect may help to explain the

lack of a TSH response in PCB-treated animals even though T4 may be reduced to 50% or less of normal levels, but introduces another level of complexity and potential interactions. The action may be related to the well-known effect of labile, *ortho*-rich PCBs on calcium regulation [15]. Calcium is essential for secretion of nearly all hormones from endocrine glands [2].

CB 110 is another congener very rapidly metabolized by mammals, while CB 153 is a persistent PCB. Both are strong PB-type inducers and deplete serum T4 at 2 daily doses of greater than 8 mg/kg; at lower doses they may cause an increase in serum T4 [7] similar to that seen with a mixture of vapor phase PCBs [13]. An elevation in serum T3 may be seen with CB 110 if a longer lag time is observed [7]. These types of relationships, along with the suppressed TSH response, can complicate interpretations of thyroid status as a function of PCB load. In a study of high-fish consuming women, there was a negative correlation between plasma CB 153 and plasma T3 [16]. If one examines the data plot, a bimodal relationship similar to that seen in rats appears to be stronger than the linear relationship examined. Nevertheless, PCB 153 was considered a Aproxy marker@ for other substances because it Ais a diortho-compound, and it is therefore unlikely@ to mediate thyroid hormone effects.

Conclusion

There are a number of factors that influence levels of circulating thyroid hormones. Both persistent and labile halogenated aromatic compounds may have bimodal dose:response effects through a number of different direct and indirect mechanisms. Some PCBs suppress the pituitary response to TRH while others suppress the thyroid response to TSH. Until these factors are understood and incorporated into interpretations of experimental as well as epidemiological data, any apparent unambiguous association between exposures to halogenated aromatic mixtures and thyroid hormone status may be coincidental. The mixture must be examined independent of former AhR dogmas and the expected responses must be adjusted for the multiple effects of each component of the mixtures.

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