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Effects of PCBs and $MeSO_2$–PCBs on adrenocortical steroidogenesis in H295R human adrenocortical carcinoma cells

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Abstract

Some endocrine disrupting chemicals (EDCs) in the environment have been shown to exert their biological effects through interference with steroidogenesis. In this study, the potential effects of four selected polychlorinated biphenyl (PCB) congeners (PCB101, PCB110, PCB126 and PCB149) as well as several of their environmentally-relevant methylsulfonyl-($MeSO_2$–) PCB metabolites (3′-$MeSO_2$–CB101, 4′-$MeSO_2$–CB101, 4′-$MeSO_2$–CB110, 3′-$MeSO_2$–CB149 and 4′-$MeSO_2$–CB149) on adrenocortical steroidogenesis were evaluated by in vitro bioassay based on the human adrenocortical carcinoma H295R cell line. The PCBs included in the study represented different structures and potential mechanisms of action. Cells were exposed for 48 h to 10 μM of each PCB congener in the presence or absence of 20% (w/w) of their corresponding $MeSO_2$–PCB metabolite(s). After the chemical treatments, changes in mRNA expression of 11 steroidogenic genes (CYP11A, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, 3β-HSD1, 3β-HSD2, 17β-HSD1, StAR and HMGR) were quantified using molecular beacon-based real-time RT-PCR. Genes coding for enzymes involved in the later or final steps of steroid production (CYP11B1, CYP11B2, CYP19, 3β-HSD1, 3β-HSD2 and 17β-HSD1) were up-regulated to various extents by most PCBs. The greatest transcriptional activations (2.8–29.9-fold) were elicited by PCB110 on CYP11B1, CYP11B2, 3β-HSD2 and CYP19, and PCB149 on CYP11B1, 3β-HSD1 and 17β-HSD1. Increased expression of these steroidogenic genes might ultimately lead to a change in hormonal balance through excessive production of steroid hormones including aldosterone, cortisol and estradiol. In addition, co-treatment with 3′- and 4′-$MeSO_2$–PCB149 resulted in a significant decrease in PCB149-induced 3β-HSD1 and 17β-HSD1 expression. This result indicates that some PCB congeners and their $MeSO_2$-metabolites may affect steroidogenesis via different

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mechanisms. Overall, these findings suggest that PCBs and PCB metabolites can affect regulation of adrenocortical steroidogenesis.
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1. Introduction

Polychlorinated biphenyls (PCBs) are one of the most ubiquitous and persistent groups of endocrine disrupting chemicals (EDCs) in the environment. Many of their effects are known to be receptor-mediated, and studies have demonstrated that PCBs can have both agonistic and antagonistic effects on the estrogen and androgen receptors, ER and AR, respectively (reviewed by Ulrich and Stahlmann, 2004), as well as effects that are mediated by the aryl hydrocarbon receptor (AhR). In general, effects of PCB on the ER are dependent on chlorination, with less chlorinated PCBs (<48% chlorine content) such as Aroclor 1248, 1242, etc., acting as estrogen mimics, and the heavily chlorinated PCBs such as Aroclor 1254, 1260, 1262, 1268 and 4465 acting as estrogen antagonists (reviewed by Foster, 1995). Similarly, PCBs have been reported to be AR antagonists, although Aroclor 1254 has also been demonstrated to be a weak AR agonist (reviewed by Ulrich and Stahlmann, 2004).

In terms of AhR activity, some PCB congeners are structurally analogous to polychlorinated-dibenzo-*p*-dioxins while others are not. Congeners that are structurally similar to the dioxins are those that are not chlorinated in the *ortho* positions, which are often referred to as the coplanar congeners as they can achieve a coplanar configuration that allows them to bind with high affinity to the AhR. Alternatively, di-*ortho*-substituted congeners do not bind to the AhR, but act through different mechanisms of toxic action (Giesy and Kannan, 1998; van den Berg et al., 1998). PCB binding to the AhR can also result in antiestrogenic effects due to cross-talk between the AhR and the ER (Safe et al., 1998).

In addition to these receptor-mediated processes, PCBs have also been shown to alter or inhibit hormone production by steroidogenic tissue in reproductive organs (Andric et al., 2001; Gregoraszczuk and Wojtowicz, 2002; Fukuzawa et al., 2003). For example, Aroclor 1248 and 1260 interrupted testicular steroidogenesis in rats through the inhibition of 3β-hydroxysteroid dehydrogenase (3β-HSD), which catalyzes the conversion of pregnenolone to progesterone (Andric et al., 2001). Aroclor 1254 significantly reduced the overall conversion of progesterone to other steroid products in guinea pig adrenal microsomes, largely via the inhibition of 21-hydroxylase activity (CYP 21) (Goldman and Yawetz, 1992). Moreover, PCB126 stimulated basal aldosterone synthesis in human adrenocortical carcinoma H295R cells with concomitant activation of the CYP11B2 gene (Li et al., 2004). In some mammals, PCBs have been found to accumulate in the adrenal gland (Berlin et al., 1975; Brandt, 1977; Biessmann, 1981; Sinjari et al., 1998), an observation which raises the possibility that PCBs can also interfere with steroidogenesis in the adrenal cortex, although this aspect has not been thoroughly studied.

Although PCBs are resistant to biodegradation, some congeners are known to undergo various degrees of in vivo biotransformation (James, 2001). The first step of the multiple biotransformation pathways is the introduction of oxygen via the cytochrome P450 (CYP) enzyme system, producing a hydroxylated metabolite (HO-PCB) or an epoxide. The epoxide can further rearrange to give a HO-PCB or a sulfur-containing metabolite such as mercapturic-, thiol-, methylsulfinyl- or methylsulfonyl- ($MeSO_2$–) PCBs. HO-PCBs are susceptible to conjugation reactions resulting in excretion, but a few are retained in blood as a consequence of their high affinity for the thyroid transport protein transthyretin (TTR) (Chauhan et al., 2000; Letcher et al., 2000, 2004). $MeSO_2$–PCBs, which are more hydrophobic and resistant to further biodegradation than HO-PCBs, accumulate in lipid-containing tissues such as the liver, lung and kidney and typically represent 5–20% of the total PCBs content in these tissues (Brandt and Bergman, 1987; Bergman et al., 1992, 1994; Letcher et al., 1995, 1998, 2000; Stapleton et al., 2001; Larsson et al., 2002; Sandala et al., 2004). The concentrations of total $MeSO_2$–PCBs in tissue samples, which are mainly reported in the fat of marine mammals, are generally in the range of 7–800 ng/g (lipid weight) (Letcher et al., 2000). To our knowledge, there have been no reports of $MeSO_2$–PCB residue levels in adrenal glands.

$MeSO_2$–PCBs, like HO-PCB's, are potential endocrine disruptors. Exposure to $MeSO_2$–PCBs competitively inhibited CYP11B1-dependent corticosterone synthesis in mouse adrenocortical Y1 cells while their parent PCBs did not (Johansson et al., 1998). Environmentally-relevant $MeSO_2$–PCB concentrations have also been shown to inhibit estradiol-mediated induction of vitellogenin in primary carp hepatocytes (Letcher et al., 2002). The existence of persistent PCB metabolites in tissues, and the fact that they differ from their parent compounds in terms of physicochemical properties and

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