Early weaning PCB 95 exposure alters the neonatal endocrine system: thyroid adipokine dysfunction

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Abstract
Polychlorinated biphenyls (PCBs) are persistent environmental pollutants that can severely disrupt the endocrine system. In the present study, early-weaned male rats were administered a single dose of 2,3,6-2',5'-pentachlorinated biphenyl (PCB 95; 32 mg/kg per day, by i.p. injection) for two consecutive days (postnatal days (PNDs) 15 and 16) and killed 24 and 48 h after the administration of the last dose. Compared with the control group, administration of PCB 95 induced a reduction \((P < 0.01)\) in serum concentrations of thyroxine, triiodothyronine, and GH and an increase \((P < 0.01)\) in the serum concentration of TSH at PNDs 17 and 18. These conspicuous perturbations led to some histopathological deterioration in the thyroid gland characterized by follicular degeneration, edema, fibrosis, hemorrhage, luminal obliteration, and hypertrophy with reduced colloid contents at PND 18. The dyshormonogenesis and thyroid dysgenesis may be attributed to the elevation of DNA fragmentation at PNDs 17 and 18. Furthermore, this hypothyroid state revealed higher \((P < 0.01)\) serum concentrations of leptin, adiponectin, and tumor necrosis factor and lower \((P < 0.01)\) serum concentrations of IGF1 and insulin at both PNDs compared with the control group. Interestingly, the body weight of the neonates in the PCB 95 group exhibited severe decreases throughout the experimental period in relation to that of the control group. These results imply that PCB 95 may act as a disruptor of the developmental hypothalamic–pituitary–thyroid axis. Hypothyroidism caused by PCB 95 may impair the adipokine axis, fat metabolism, and in general postnatal development. Thus, further studies need to be carried out to understand this concept.

Key Words
- PCB 95
- thyroid
- adipokines
- rat newborns

Introduction
Polychlorinated biphenyls (PCBs), a xenobiotic group of halogenated aromatic hydrocarbons, are the most hazardous, widespread, persistent, and ubiquitous environmental contaminants (Persky et al. 2012, Grimm et al. 2013, Murk et al. 2013). A large number of PCB congeners, about 209 PCBs, are produced and used in industrial materials and domestic products worldwide (Zoeller et al. 2002), and their toxicological properties depend on the number and position of chlorine substitutions (Leijs et al. 2012). In the United States, PCBs are manufactured as complex mixtures under the trade name Aroclor with a designation indicating the extent of chlorination (Karcher et al. 2004). The U.S. Environmental Protection Agency also recognizes PCBs as unavoidable toxins (2010 21CFR109.30.), because dairy products, meat, and fish are their sources (Persky et al. 2012, Grimm et al. 2013).
These organohalogenes are also bioaccumulated and biomagnified in the food chain and in the biological tissues to levels that are associated with a variety of health effects in human and animals (Miller et al. 2012). These potential effects are amplified and increased during development (Koibuchi & Iwasaki 2006). Furthermore, in humans, they are mainly stored in the adipose tissue, with elimination half-lives of 6–10 years (Norstrom et al. 2010).

Importantly, the thyroid axis appears to be vulnerable to disruption by PCBS (Munk et al. 2013) and PCB metabolites (Sinjari & Darnerud 1998), particularly during development, because most of these polyhalogenated hydrocarbons have the kinetics of highly lipid-soluble substances (Crofton et al. 2000b). Epidemiological studies have suggested that PCBS may affect growth and development by impairing thyroid function (Koopman-Esseboom et al. 1994, Kobayashi et al. 2009). However, their effects and precise toxicological mechanism(s) during development remain unclear. On the other hand, in animal and human studies, PCBS have been shown to disrupt adiponectin (Mullerova et al. 2008), leptin (Niiminen et al. 2000), tumor necrosis factor (TNF-α; Arsenescu et al. 2008), and insulin (Everett et al. 2011) concentrations, body weight, energy expenditure and fat depots (Anbalagan et al. 2003). However, studies on possible interactions between PCBS and adipokine concentration changes associated with thyroid dysfunction during the early weaning period are scarce.

As exposure to environmental contaminants is more likely to cause endocrine disturbances in neonates than in adults (Crofton 2004, Kobayashi et al. 2009), the aim of this study was to assess the effect of 2,3,6-2',5'-pentachlorinated biphenyl (PCB 95), a toxic noncoplanar PCB congener (Schantz et al. 2003), on aspects of development of the thyroid axis and adipokine markers in albino rats at the early weaning period, particularly at postnatal days (PNDs) 17 and 18.

**Materials and methods**

**Animals and treatments**

The experimental animals used in this study were male white albino rats (24 pups aged 15 PND). The rats were obtained from the National Institute of Ophthalmology, Giza, Egypt. They were housed in cages and randomly divided into two groups: control and PCB 95. They were fed a standard rodent pellet diet manufactured by an Egyptian company producing oil and soap as well as some vegetables as a source of vitamins (Ahmed et al. 2010, El-bakry et al. 2010). Tap water was provided and the rats allowed to drink *ad libitum*. The rats were exposed to constant daily 12 h light:12 h darkness each (lights on at 0600 h) and 50±5% relative humidity (Ahmed & Incerti 2013). Generally, all the animal procedures were in accordance with the general guidelines of animal care and the recommendations of the Canadian Council on Animal Care (CCAC; Olfert et al. 1993). All efforts were made to minimize the number of animals used and their suffering.

The pups were given a single dose of PCB 95 (Sigma-Aldrich; 32 mg/kg per day, by i.p. injection) (Khan et al. 2002) for 2 consecutive days and killed 24 and 48 h after the administration of the last dose. At PNDs 17 and 18, the newborns were subsequently killed under mild diethyl ether anesthesia, and blood samples were collected and centrifuged at 1006.2 g for 30 min. Clear, nonhemolyzed supernatant sera were removed quickly, divided into three portions for each rat, and kept at −30°C until use for different developmental and biochemical assays. The thyroid glands were removed and directly dissected on ice, washed with saline, patted dry on a filter paper, and weighed. The thyroid glands from three rats were pooled and homogenized in cold phosphate buffer (pH 7.4, 20 mM) (Mutaku et al. 1998) using a Teflon homogenizer (Glas-Col, Terre Haute, IN, USA). The thyroid homogenates were used for the DNA fragmentation assay. The thyroid glands of other rats were fixed in 10% neutral buffered formalin for study of the general histological structure (hematoxylin and eosin stain; Bancroft & Stevens (1982)). Thyroid slides were examined under a light microscope for the presence of any histological changes. All reagents were of the purest grades commercially available.

**RIA examination**

The serum concentrations of thyroxine (T₄), triiodothyronine (T₃), thyrotrophin (TSH), growth hormone (GH), and insulin-like growth factor 1 (IGF1) were estimated quantitatively by RIA at the Diabetic Endocrine Metabolic Pediatric Unit, Center for Social and Preventive Medicine, New Childrens Hospital, Faculty of Medicine, Cairo University, Egypt, according to the method of Thakur et al. (1997) for T₄, Maes et al. (1997) for T₃, Mandel et al. (1993) for TSH, Reutens (1995) for GH, and Dauncey et al. (1993) for IGF1. The kits were obtained from Calbiotech, Inc. (Spring Valley, CA, USA).

**Histological examination of the thyroid glands of neonates**

Some thyroid tissue samples, intended for histological examination by light microscopy, were immediately fixed...
in 10% neutral buffered formalin solutions and processed through a series of graded ethanol solutions. They were then embedded in paraffin, serially sectioned at 6 μm, and stained with hematoxylin–eosin at the National Cancer Institute, Cairo University, Egypt. The sections were cut parallel to the longitudinal axis of the trachea and were evaluated for the degree of thyroid injury.

Biochemical examination of the thyroid glands of neonates

The extent of DNA fragmentation was determined by the method adapted from that of Lin et al. (1997) and Shagirtha et al. (2011). Thyroid tissue homogenates were treated with 0.01 M Tris buffer (pH 8.0), 1 mM EDTA, and 0.5% Triton X-100 and centrifuged at 1006.2 g for 20 min. Both the supernatant and pellet were precipitated with 12.5% TCA. Quantitative analysis of DNA was carried out by diphenylamine reaction. The percentage of fragmentation was calculated from the ratio of DNA in the supernatant to the total DNA.

ELISA examination

The serum concentrations of leptin, adiponectin, TNFα, and insulin were determined by an immunoassay using a microplate reader (Spectra Max 190 – Molecular Devices, Sunnyvale, CA, USA) in my department laboratory. Commercial kits were used for the measurement of the concentrations of leptin, insulin, and adiponectin (ELISA kit – Millipore, St Charles, MO, USA). The TNFα ELISA kit was purchased from Invitrogen Corporation.

Statistical analysis

Data were analyzed using one-way ANOVA (PC-STAT, version 1A; University of Georgia, Athens, GA, USA) followed by least significant difference (LSD) analysis to determine the main effects and compare the groups with each other. F probability for each variable expresses the general effect between the groups. The data are presented as means ± S.E.M., and values of P < 0.01 and P < 0.001 were considered statistically highly significant and very highly significant respectively.

Results

Neonatal serum thyroid markers

The concentrations of T4, T3, TSH, and GH in the control group increased gradually from PND 17 to PND 18 (Fig. 1).

Histological changes and DNA fragmentation in the thyroid glands of neonates

The thyroid glands of the control pups exhibited normal distribution, morphology, and architecture of follicles and parafollicular cells at PND 18 (Fig. 2A). The lumina of these follicles varied from irregular rounded to tubular shape and had a single layer of cuboidal cells lining the epithelium. The administration of PCB 95 led to some subtle histopathological alterations in these follicles. The follicles were extremely damaged, and their lumina exhibited a severe degree of degeneration (Fig. 2B). Most of these follicles were enlarged with decreased colloidal contents in their lumina. There was also marked fibroblast proliferation between the follicles, hemorrhage, edema, and luminal obliteration at PND 18. Importantly, the follicles became very irregular and abnormal, also PCB 95 administration...
led to thyroid dysgenesis. On the other hand, the administration of PCB 95 increased the extent of DNA fragmentation from 8.42-fold at PND 17 to 9.55-fold at PND 18 when compared with the age-matched control group (Fig. 3). The general effect between the groups, on the DNA fragmentation at all the tested PNDs, was very highly significant \( (P < 0.001) \), as evaluated by one-way ANOVA.

Neonatal serum adipokine markers, insulin, IGF1, and body weight

In the control group newborns, the gradual increase in the concentrations of leptin, adiponectin, and TNF\(\alpha\) was associated with a profound increase in body weight from PND 17 to PND 18 (Figs 4 and 5). In the PCB 95-treated group, the concentrations of leptin, adiponectin, and TNF\(\alpha\) were increased \( (P < 0.01) \) by 1.8-, 13.41-, and 9.3-fold respectively, while those of insulin and IGF1 were reduced \( (P < 0.01) \) by 0.4- and 2-fold respectively at PND 17 in comparison with the control group (Fig. 4). In addition, the concentrations of leptin, adiponectin, and TNF\(\alpha\) were found to be increased by 2.95-, 22.3-, and 18.36-fold respectively, although the concentrations of insulin and IGF1 were found to be decreased by 1.42- and 4.4-fold respectively in the PCB 95-treated group at PND 18 when compared with the control group (Fig. 4). Interestingly, the administration of PCB 95 induced a maximal increase in the concentration of adiponectin at PND 18. Conversely, PCB 95 administration had a severe effect on the concentrations of insulin and IGF1, where their percentage index dropped from 50 and 59.70% at PND 17 to 94.66 and 87.12% at PND 18 respectively. On the other hand, the results indicate that the body weight of PCB 95-treated group newborns was lower \( (P < 0.01) \) than that of the control group newborns at PNDs 17 (28.30%) and 18 (65.00%) (Fig. 5). Based on one-way ANOVA of these parameters, it was found that the general effect between the groups was very highly significant \( (P < 0.001) \) throughout the experiment.

Discussion

The data presented herein clearly demonstrate the elevation in the serum concentrations of \( T_4, T_3, TSH, GH, \) and IGF1 in the control group at PNDs 17 and 18. These observations are largely congruent with several
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Previously published results. The concentrations of thyroid hormones (THs; El-bakry et al. 2010, Saranac et al. 2013), TSH (Ahmed 2011, Ahmed et al. 2012a), and GH (Zimmermann 2011, Ahmed 2012) in neonates increase steadily until the thyroid gland is fully developed at the end of the fourth postnatal week (Ahmed et al. 2008). The serum concentration of IGF1 might also increase during the different growth periods (Kursunluoglu et al. 2009). These elevations may reflect the normal appearance of thyroid tissue and intact follicular structure as recorded in the present study. This in turn confirms that the gradual increase in the concentrations of TSH (Jahnke et al. 2004, Ahmed & Incerpi 2013), GH (Ahmed 2011), and IGF1 (Kursunluoglu et al. 2009) is necessary for the development and growth of this gland.

In the present study, a significant increase in the serum concentrations of leptin, adiponectin, TNFα, insulin, and IGF1 (expressed in ng/dl) of the control and PCB 95-treated newborns during the postnatal period. Bars represent means ± S.E.M. of six rats/group, where the change between both the groups/PND is highly significant (**P < 0.01) as determined by LSD analysis. ANOVA (F probability) indicates that the effect between the groups and tested PNDs is very highly significant (P < 0.001).

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concentrations of T₄ and T₃ and a significant increase in the serum concentration of TSH at PNDs 17 and 18 when compared with the control group. PCB 95 administration also significantly increased DNA fragmentation in the thyroid glands of the neonates during the experimental period.

Similarly, treatment with PCBs leads to distinct histopathological changes in the thyroid gland (Tang et al. 2013), such as hyperplasia of the follicular epithelium, colloidal content reduction, vascularization, and lymphocyte infiltration in perifollicular areas (Gu et al. 2009). Furthermore, there is substantial evidence that perinatal exposure to PCBs and their hydroxylated metabolites decreases the concentrations of THs in the offspring (Crofton et al. 2000a,b, Meerts et al. 2002, Boas et al. 2012). Exposure to PCBs induces hypothyroidism (decreases the concentrations of THs and increases those of TSH) in rats (Khan et al. 2002, Powers et al. 2006), sled dogs (Kirkegaard et al. 2011), monkeys (Boas et al. 2006), and children living near PCB-contaminated sites (Schell et al. 2004). Additionally, the elevation in DNA fragmentation reported herein is consistent with results of previous laboratory experiments showing that PCBs have the ability to break DNA strands (Ahlborg et al. 1992), where they may directly act on the thyroid receptor (TR) to modulate its action or indirectly act on an unknown TR-binding protein, which may then lead to conformational changes in the TR-DNA-binding domain to dissociate TR from the T₃-responsive element (TRE; Miyazaki et al. 2008). Such lesions presumably contribute to altered thyroid function, leading to hypothyroidism (dyshormonogenesis). These explanations strengthen the possibility that the administration of PCB 95 may pose a significant risk for the pituitary–thyroid axis and this may lead to adverse developmental effects.

Collectively, results reported by many authors (Crofton & Zoeller 2005, Miller et al. 2009, Patrick 2009, Grimm et al. 2013) indicate the following mechanisms to be involved in the impairment of thyroid function by PCBs: i) PCBs may reduce the ability of THs to bind to the transport proteins (transthyretin) in the bloodstream; ii) PCBs may impair the proteolysis of thyroglobulin; iii) PCBs may activate the aryl hydrocarbon receptors (AhRs), resulting in the elevation of the concentrations of several hepatic enzymes, including uridine diphosphate glucuronoyl transferases and sulfotransferases; iv) PCBs may activate phase II conjugation of T₄ (formation of T₄-glucuronide (T₄-G)), resulting in the elevation of biliary excretion of T₄-G and reduction in the circulating concentration of T₄, leading to hypothyroidism; v) PCBs may inhibit or upregulate the production of deiodinases that allow T₄ to be converted to T₃; and vi) PCBs may act as either an agonist or an antagonist at the site of the cellular TR, where they induce a partial dissociation of TR/retinoid X receptor (RXR) heterodimer complex from the TRE, resulting in the suppression of gene transcription. Although it is not clear which among these potential mechanisms are most important for mediating the effects of PCBs on the circulating concentrations of THs, it is likely that all are important to some extent in experimental models.

In the present study, a significant decrease in the serum concentrations of GH and IGF1 in the PCB 95-hypothyroid group was observed at PNDs 17 and 18 in comparison with the control group. Several studies have found that prenatal exposure to PCBs leads to a decrease in the concentration of THs along with growth retardation in rat offspring (Bowers et al. 2004) and in infants (Koopman-Esseboom et al. 1994). This may be due to the loss of anabolism during hypothyroidism (Robson et al. 2002). Concurrently, hypothyroidism is associated with a significant decrease in the activities of IGF1 (Akin et al. 2009) and the GH/IGF1 axis (Ramos et al. 2001). Interestingly, the reduction in the concentration of GH can be attributed to the disruption of the activities of THs (Ahmed 2012), of the synthesis and release of growth hormone-releasing hormone (GH-RH), of the sensitivity of the pituitary gland to GH-RH, and of the transcription of the GH gene (Osfor et al. 2013). It has also been shown that the effects of THs on IGF1 synthesis and secretion are mediated by insulin in neonatal hypothyroid rats (Ramos et al. 2002). These findings are concomitant with those of the present study, where the depletion in the concentration of IGF1 was related to the alterations in the activities of THs and insulin that may delay growth. These findings imply that PCB 95 may disturb the GH/IGF1 axis during the postnatal period via the thyroid axis.

On the other hand, the serum concentrations of leptin, adiponectin, and TNFz were highly significantly increased even though the serum concentration of insulin was highly significantly decreased in the PCB 95-hypothyroid group at both the examined PNDs in comparison with the corresponding control group. In particular, the administration of PCB 95 at PND 18 led to a maximal increase in the concentration of adiponectin and the highest drop in the concentrations of insulin and IGF1, respectively. This is probably due to the disturbance of the hormonal homeostatic mechanisms on this day.

The results of the present study are in concordance with those of the study carried out by Chen et al. (2000)
and Mazaki-Tovi et al. (2010), who demonstrated hyperleptinemia in the hypothyroid state. This state might be explained by the reduction in leptin turnover and degradation (Houseknecht et al. 1996) or stimulation of the HPTA in response to low TH concentrations in rats, dogs, and humans (Mazaki-Tovi et al. 2010). In contrast to these results, the serum concentration of leptin was found to be decreased during hypothyroidism (Ahmed et al. 2012b). Nieminen et al. (2000) also reported that subchronic exposure to PCBs has no effect on the plasma concentration of leptin. This discrepancy could be due to the experimental models, developmental period, and animal species used.

Moreover, in low TH concentration states, the serum concentration of adiponectin has been shown to increase significantly (Kokkinos et al. 2007), while the response of insulin to glucose has been shown to be delayed (Robson et al. 2002). The evidence reported by these authors is in agreement, to a large extent, with the results of the present study. In general, alterations in glucose and insulin metabolism due to PCBs and dioxins may be mediated by AhRs (Craft et al. 2002, Everett et al. 2011, Baker et al. 2013). In contrast to the findings of the present study, a negative correlation has been found between adiponectin concentration and PCB 153 (Mullerova et al. 2008), 3,3′,4,4′-tetrachlorobiphenyl (PCB 77; Arsenescu et al. 2008), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; Kern et al. 2004), and bisphenol A (BPA; Kidani et al. 2010). On the basis of these results, it is possible that the controversy about these markers may reflect the thyroid dysfunction due to PCB 95.

Furthermore, data reported herein support a positive association between serum TNFα concentration and weaning exposure to PCB 95. Previous studies have postulated that the exposure to coplanar PCB 77 (a ligand of AhR) (Arsenescu et al. 2008, Baker et al. 2013), BPA (Ben-Jonathan et al. 2009), or a full mixture of PCB, organochlorine pesticides, and methylmercury (Hayley et al. 2011) promotes the production of proinflammatory adipokines, such as TNFα and interleukins (IL6 or IL12). The concomitant increase in the concentration of TNFα with a decreased activity of insulin, in the present study, may also be responsible for HPTA dysfunction. This might reflect the activation of AhR by PCBs (Crofton & Zoeller 2005).

In the present study, it was found that the administration of PCB 95 resulted in a substantial decrease in the body weights of neonates at PNDs 17 and 18 when compared with those of members of the control group. These results are in agreement with a previous laboratory experiment showing that a lower dose of Aroclor 1254 (200 μg/kg per day) (Anbalagan et al. 2003) or a higher dose of BPA (Nunez et al. 2001) induces a significant decrease in the body weight, fat depots, and feeding efficiency of rats. In immature rats and infants, low body weight during hypothyroidism is associated with reduced concentrations of serum GH, IGF, and carrier protein (Burstein et al. 1979). This could be attributed to the fact that THs (Ahima & Flier 2011), leptin (Rosenbaum et al. 2005), and adiponectin (Qi et al. 2004) play a role in the reduction of body fat mass and body weight by stimulating energy expenditure and lipid oxidation. The loss of body weight may suggest a decline in the general health level of animals (Fernandes et al. 2007), which can be important in the interpretation of thyroid effects (Ahmed et al. 2008).

**Conclusion**

Five conclusions can be drawn from these data. The first is that the developmental exposure to PCB 95 in the early weaning period seems to alter TH synthesis and secretion, either by acting directly on the thyroid gland or by acting on the pituitary or hypothalamic control of TSH or GH/IGF1 secretion. The second is that the administration appears to induce hypothyroidism via thyroid dysgenesis and dyshormonogenesis. These drastic effects may play a significant role in thyroid diseases. The third is that PCB 95 seems to play the role of a stress-responsive factor in the neonatal endocrine system (HPTA). The fourth is that hypothyroidism caused by PCB 95 seems to alter the development of the adipokine axis, fat metabolism, and in general postnatal development. The final conclusion is that the administration of PCB 95 seems to lead to thyroid adipokine dysfunction (Fig. 6). These changes
may be either directly or indirectly related to TH action. More interestingly, the toxicity of PCBs is dependent on compound congeners, dose, exposure duration, developmental period, and the species involved. From this, it can be concluded that the endocrine-disrupting compounds can exert complex, mosaic effects during an animal’s life cycle (Zoeller et al. 2012). Further investigations are required to elucidate the potential associations with human health.

Future direction

– Studies focusing on the direct relationship between HPTA and fat tissue are needed to clarify the development-mental interactions between thyroid function status and adipokines. Future research should also determine the dose of PCBs received by developing rats from placental and lactation exposure, as well as the hepatic catabolic responses of developing neonates to PCBs, to explain the lack of effects of PCBs at later postnatal ages.

– Longitudinal studies of the developmental neuroendo-crine system in newborns/infants should be carried out in fish-eating populations because fish is a major source of PCBs. Any degree of thyroid disruption that affects the concentrations of THs on a population basis should be considered a biomarker of adverse outcomes, which may have important societal effects (Miller et al. 2009).

– Future studies also need to elucidate important interactions among contaminants, hormones, protein expression, and other phenotypic or physiological measures to gain understanding of what factors – or groups of factors – are driving phenotypic changes in animals living in affected environments.

Declaration of interest
The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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