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Perinatal TCDD exposure alters developmental neuroendocrine system

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ABSTRACT

This study tested whether maternal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) may disrupt the development of neuroendocrine system of their offspring during the perinatal period. TCDD (0.2 or 0.4 μg/kg body weight) was orally administered to pregnant rats from gestation day (GD) 1 to lactation day (LD) 30. Potential effects on neuroendocrine function were evaluated by measuring serum thyroid hormone levels in pregnant rats and their offspring and measuring some biochemical parameters in cerebellum of these offspring on GD 16 and 19, and LD 10, 20, and 30. In both treated groups, a decrease in serum thyroxine (T4), triiodothyronine (T3) and increase in thyrotropin (TSH) levels were noticed during the tested days in dams and offspring, as well as GH levels were decreased in offspring with respect to control group. In cerebellum of control offspring, the levels of monoamines, γ-aminobutyric acid (GABA) and acetylcholinesterase (AchE) were found to be increased from GD 16 to LD 30. The hypothyroid conditions due to both maternal administrations of TCDD produced inhibitory effects on monoamines and AchE, and stimulatory actions on GABA in cerebellum of offspring. These alterations were dose and age dependent. Overall, these results suggest that TCDD may act as neuroendocrine disruptor.

1. Introduction

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is a potent environmental and developmental toxicant (Tanida et al., 2009; Darnerud et al., 2010; Goodman et al., 2010; Matsumoto et al., 2010). It belongs to polychlorinated aromatic hydrocarbons (PAHs) group, which include polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-*p*-dioxins (PCDDs) (Koibuchi, 2006; Hennig et al., 2007; Nishijo et al., 2007; Brouillette and Quirion, 2008; Crofton, 2008; Darras, 2008; Sul et al., 2009; Tanida et al., 2009; Darnerud et al., 2010; Goodman et al., 2010; Matsumoto et al., 2010). These organohalogens are bioaccumulated and biomagnified in the food chain, meat and milk products (including breast milk) (Hassoun et al., 2000; Darnerud et al., 2010), and in the tissues of wildlife, domestic and marine animals and human's worldwide (Gilbert, 2003; Ishida et al., 2005; Charnley and Kimbrough, 2006; Hennig et al., 2007; Brouillette and Quirion, 2008; Smith et al., 2008; Tanida et al., 2009). Particularly, TCDD is an unintentional by-product of multiple anthropogenic processes such as bleaching using chlorine gas, combustion and incineration of wastes (municipal, hospital, hazardous), fabrication of pesticides and herbicides, wood products, tobacco smoke, production of iron and steel, coal-fired electric power generation, photochemical and enzymatic reactions in sewage sludge (Viluksela et al., 2004; Hood et al., 2006; Smith et al., 2008; Tanida et al., 2009; Darnerud et al., 2010). TCDD has a long half-life in animals (Byers et al., 2006) and in humans (approximately 8 years) (Byers et al., 2006; Goodman et al., 2010).

Due to the high lipophilicity and relatively slow metabolism of TCDD, this compound accumulates in maternal fat stores and cross the placenta (Kreuzer et al., 1997; Mori, 2001; Petersen et al., 2006; Nishijo et al., 2007; Tanida et al., 2009) to produce a wide variety of toxic effects in offspring (Kuchiiwa et al., 2002) as a permanent brain damage (Petersen et al., 2006). Dioxin affects the development of offspring during embryonic and fetal periods even when the exposure level is too low to induce toxicity in the mother (Mably et al., 1992). In Europe and USA, perinatal exposure to background levels of dioxins cause persistent effects during childhood (ten Tusscher and Koppe 2004). These effects may be related to alterations in thyroid functions (Takser et al., 2005; Wang et al., 2005; ten Tusscher et al., 2007; Leijs et al., 2008; Pearce and Braverman, 2009) which are essential for normal development in utero and in infancy (Bruno et al., 2005; Gilbert and Sui, 2006; Carageorgiou et al., 2007; Ahmed et al., 2008; Koibuchi, 2008; Leonard, 2008; Shibutani et al., 2009; Wirth et al., 2009; Zhang et al., 2009; Davis et al., 2010; Di Paola et al., 2010; Fu et al., 2010; Jugan et al., 2010; Sigrun and Heike, 2010). However, another investigation failed to show associations between dioxins and THs in maternal serum of pregnant women (Foster et al., 2005).

THs are strongly involved in vertebrate brain development, from early embryogenesis to subsequent prenatal and perinatal development particularly in mammals (Bruno et al., 2005; Gilbert and Sui, 2006; Carageorgiou et al., 2007; Ahmed et al., 2008; El-bakry et al., 2010; Horn and Heuer, 2010; Jugan et al., 2010).

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Also, the developing brain is very sensitive to TCDD exposure (Markowski et al., 2002; Kakeyama and Tohyama, 2003; Kim et al., 2007) where the maternal exposure delayed the fetal brain growth and neurodevelopment in offspring of rat (Nishijo et al., 2007) and of non-human primates (Schantz et al., 1992; Negishi et al., 2006). These alterations might cause subtle but profound and irreversible deficits in brain functions in adulthood (Negishi et al., 2006). The interference mechanism of persistent organic pollutants (dioxin) with THs metabolism in the mother, fetus and newborn may injure the developing brain (Porterfield, 2000; Winneke et al., 2002; ten Tusscher and Koppe, 2004; Roelens et al., 2005; Grandjean and Landrigan, 2006; Brouillette and Quirion, 2008), even at background environmental levels (Darras, 2008), via the availability of TH transporters (Friesema et al., 2005, 2010; Heuer et al., 2005; Nunez et al., 2008). Also, several hypotheses linking the mechanisms of TCDD neurotoxicity with the alterations of central monoaminergic, glutamatergic and cholinergic systems have been proposed. TCDD exposure (Pohjanvirta and Tuomisto, 1994) and THs dysfunction (Mason et al., 1990) may alter various neurotransmitter systems (Hassoun et al., 2000), particularly biogenic amines (Porterfield, 2000). More so, PCB may alter γ-aminobutyric acid (GABA)-mediated pathways (Bushnell and Rice, 1999) and may decrease the activity of choline acetyltransferase (ChAT) (Juarez de Ku et al., 1994) in the developing brain. These observations are the same as those seen in neonatally hypothyroid rats (Porterfield, 2000). However, these mechanisms are not fully understood.

Unfortunately, little is known about the neurodevelopment of dioxins, despite their impact on society. Thus, the present study aims to determine whether the exposure of pregnant white albino rats (*Rattus norvegicus*, Wistar strain) to TCDD through pre- and post-natal periods may disturb the development of neuroendocrine system, particularly the interactions between THs and development of cerebellum. Notably, TCDD was examined herein because it is the prototype dioxin-like chemical and the most potent congener (Hassoun et al., 2000). Also, rat cerebellum was used as a model system, because this region is highly sensitive to any stress (TH disturbance) during perinatal period (Koibuchi and Chin, 2000; Li et al., 2004; Yousefi et al., 2005; Ahmed et al., 2008; Koibuchi, 2009).

2. Materials and methods

2.1. Chemicals

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD; purity >99%), corn oil, norepinephrine (NE), epinephrine (E), dopamine (DA), serotonin (5-HT), γ-aminobutyric acid (GABA), thiocholiniodide, 5,5′-dithiobis-2-nitrobenzoic acid (DTNB), acetylthiocholiniodide, sodium tartrate, copper tartrate, trichloroacetic acid (TCA) and general chemicals were purchased from Sigma Chemical Company (Sigma, St. Louis, MO, USA). Thyroxine (T4), triiodothyronine (T3) and thyrotropin (TSH) kits were obtained from Diagnostic Products Corporation (DPC) (Los Angeles, USA), as well as growth hormone (GH) kit was purchased from BioSource Europe S.A. (Belgium).

2.2. Experimental animals

Mature white albino rats (*Rattus norvegicus*, Wistar strain) were purchased from the National Institute of Ophthalmology, Giza, Egypt. This study was carried out on 18 mature virgin females/group weighing about 170–190 g and 9 mature males/group for mating only. They were kept under observation in the department animal house for 2 weeks to exclude any intercurrent infection and to acclimatize the new conditions. The animals were marked, housed in metal (stainless steel; 60 × 50 × 50 cm) separate bottom ventilated cages at normal atmospheric temperature (23 ± 2 °C) and fed on standard rodent pellet diet manufactured by the Egyptian Company for oil and soap as well as some vegetables as a source of vitamins (Ahmed et al., 2007b, 2010; El-bakry et al., 2010). Tap water was used for drinking ad libitum and these animals were exposed to constant daily light/dark periods of 12 h each (lights on at 06:00 h) and 50 ± 5% relative humidity (Ahmed, 2009; Ahmed et al., 2010; El-bakry et al., 2010). All animal procedures are in accordance with the general guidelines of animal care and the recommendations of the Canadian Committee for Care and use of animals (Canadian Council on Animal Care, 1993). All efforts were made to minimize the number of animals used and their suffering.

Daily examination of vaginal smears of each virgin female was carried out to determine the estrus cycle. Estrous females exhibited the presence of cornified cells in vaginal smears. Mating was induced by housing proestrus females with male in separate cage at ratio of two females and one male overnight for one or two consecutive days. In the next morning, the presence of sperm in vaginal smears determined the first day of gestation. Then, the pregnant females were transferred into separate cages from males to start the experiment.

2.3. Experimental strategy

Non-anesthetized pregnant rats received two doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (0.2 or 0.4 μg/kg body weight) orally by gastric intubation and daily from gestation day (GD) 1 to lactation day (LD) 30 (between 7.30 and 8.30 a.m.). TCDD was dissolved in corn oil vehicle being a highly lipophilic compound (Hassoun et al., 2000; Darnerud et al., 2010). Oral administration of TCDD is the most likely route of entry into the animal in natural conditions and the doses were selected based on preliminary dose–response studies. TCDD (0.2 μg/kg) was the concentration giving the lowest adverse effect observed while 0.4 μg/kg TCDD was the highest dose giving adverse effect (no obvious signs of developmental toxicity). Corn oil vehicle only was orally administered to control group by gastric intubations. Dams and their offspring were decapitated under mild diethyl ether anesthesia and sampled at GD 16 and 19, and at LD 10, 20, and 30.

The mother blood samples (6 per group) were taken from jugular vein during the gestational period at day 16 and 19 and lactational period at day 10, 20 and 30. Fetal blood samples (6 per group) were collected directly from the umbilical cord at GD 16 and 19 while the pup's blood samples were taken from jugular vein at postnatal day (PND) 10, 20 and 30. The clotted blood samples were centrifuged at speed 3000 rpm (1006.2*g*) and at temperature 15–24 °C for 30 min. The clear, non-hemolysed supernatant sera were quickly removed, divided into three portions for each individual animal, and kept at −30 °C until use for different hormonal assays (radioimmunoassay). On the other hand, cerebellum of rat offspring was quickly removed, separated and homogenized by using a Teflon homogenizer (Glas-Col, Terre Haute in USA), and kept in deep freezer at −30 °C until use for different developmental and biochemical assays.

2.4. The radioimmunoassay examinations

T4, T3 and TSH in serum of mothers and their offspring, as well as GH in serum of their offspring only were estimated according to the method of Thakur et al. (1997), Maes et al. (1997), Mandel et al. (1993) and Reutens (1995), respectively.

2.5. The developmental and biochemical examinations in cerebellum of offspring

2.5.1. High performance liquid chromatography (HPLC) analysis

2.5.1.1. Estimation of monoamines concentrations. The monoamines concentrations were estimated according to the method of Pagel et al. (2000). Cerebellum was homogenized in 75% aqueous HPLC grade methanol. The homogenates were spun at 3000 rpm for 15 min and the supernatants were immediately extracted from the trace elements and lipids by the use of solid phase extraction CHROMABOND column NH2 phase Cat. No. 730031. The samples were then injected directly to the AQUA column (150 × 4.6 mm, 5μ and C18) (phenomenex, USA) under the following conditions: mobile phase 97/3 20 mM potassium phosphate, pH 3.0/methanol, flow rate 1.5 ml/min, UV 270 nm. Additionally, norepinephrine, epinephrine, dopamine and serotonin were separated after 12 min, the resulting chromatogram for each sample identified each monoamines position and area under curve was compared to that of the standard curve made by Eurochrom HPLC Software, version 1.6. Calculation: Concentration of sample (μg/g) = Concentration of standard (μg/ml) × volume of homogenization/weight of tissue (g) × area of sample under curve/area of standard under curve.

2.5.1.2. Estimation of γ-aminobutyric acid (GABA) concentration. GABA concentration was determined according to the method of Chakrabarti and Poddar (1989). A 10% (w/v) homogenates were prepared in 0.25 M cold sucrose. Protein free filtrates of cerebellum homogenates were prepared by mixing the homogenates with equal volumes of 10% TCA. This was followed by centrifugation in cold at 3000 rpm for 15 min. GABA content was measured using sodium tartrate and copper tartrate, respectively, after developing fluorophores by ninhydrin with the protein-free filtrate. Calculation: Concentration of sample (μg/g) = Concentration of standard (μg/ml) × volume of homogenization/weight of tissue (g) × area of sample under curve/area of standard under curve.

2.5.2. Estimation of acetylcholinesterase (AchE) activity

The method used in this study was a modification of Ellman method (Ellman, 1978) using acetylthiocholiniodide as substrate. Add 0.1 ml homogenate in the assay system [0.15 ml phosphate buffer (20 mM, pH 7.6) and 0.05 ml substrate (0.1 M acetyl-thiocholiniodide)]. Then, the reaction was stopped by 1.8 ml

DTNB-phosphate ethanol reagent [12.4 mg DTNB was dissolved in 120 ml of 96% ethanol, 80 ml distilled water and 50 ml of 0.1 M phosphate buffer (pH 7.6)] after 10 min at 37 °C. The developed color was measured immediately at 412 nm.

2.6. Statistical analysis

The data are analyzed using one-way analysis of variance (ANOVA) (PC-STAT, University of Georgia, 1985) followed by LSD analysis to discern the main effects and compare various groups with each other. *F*-probability for each variable expresses the general effect between groups. The data are presented as mean ± standard error (SE) and values of $P > 0.05$ are considered statistically non-significant while those of $P < 0.05$, $P < 0.01$ and $P < 0.001$ are considered statistically significant, highly significant and very highly significant, respectively.

3. Results

3.1. Serum–hormone levels

3.1.1. Effect of both maternal TCDD on dam serum

A gradual increase of thyroxine (T4), triiodothyronine (T3) and thyrotropin (TSH) levels was found in control maternal albino rats at GD 16 and 19, and at LD 10, 20 and 30 (Table 1). Both administrations of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (0.2 and 0.4 μg/kg) to pregnant rats from GD 16 to LD 30 resulted in a marked decrease (LSD; $P < 0.01$) of T4 and T3 levels and a significant increase (LSD; $P < 0.01$) of TSH levels with respect to control (hypothyroid state). These changes became more relevant at LD 30. Also, in the later period, the levels of T4 and T3 were found to be decreased about 9.93 and 2.66-fold in the 1st treated group (0.2 μg/kg TCDD) and about 16.57 and 3.75-fold in the 2nd treated group (0.4 μg/kg TCDD), respectively whereas the level of TSH exhibited about 8.45 and 17.99-fold increase in the 1st treated group and 2nd treated group, when compared to respective control values.

3.1.2. Effect of both maternal TCDD during perinatal period on offspring serum

In control offspring, the levels of T4, T3, TSH and growth hormone (GH) were increased at GD 16 and 19, and at postnatal day (PND) 10, 20 and 30 (Table 2). In offspring of both treated mothers, the baseline levels of T4, T3 and GH were markedly decreased (LSD, $P < 0.01$) while the levels of TSH were gradually elevated (LSD, $P < 0.01$) at all tested periods with respect to control group, except for T3 at GD 16 in both treated groups where the decrease in its level was non-significant (LSD, $P > 0.05$), for T3 at GD 19 and for TSH at GD 16 in the 1st treated group (0.2 μg/kg TCDD) only, where the decreases in T3 and increases in TSH levels were significant (LSD, $P < 0.05$). On the other hand, at PND 30, the value of TSH in 2nd treated group (0.4 μg/kg TCDD) was very high if compared to the levels in the age-matched normal control or 1st treated group (0.2 μg/kg TCDD) (26.53 vs. 13.01 and 19.56 ng/100 ml, respectively). Generally, the alterations of these hormones were more significant in both treated groups at the end of the experiment with respect to control group.

Table 1
Effect of different doses of TCDD in thyroid functions [thyroxine (T4, ng/100 ml), triiodothyronine (T3, ng/100 ml) and thyrotropin (TSH, ng/100 ml)] of pregnant rats during perinatal period.

Periods	TCDD (μg/kg)	Serum T4	Serum T3	Serum TSH
GD16	0	14.37 ± 0.576^{g}	$1.44 \pm 0.028^{h-i}$	5.26 ± 0.335^{g}
	0.2	10.13 ± 0.357^{h}	0.93 ± 0.029^{j}	8.33 ± 0.158^{f}
	0.4	7.35 ± 0.326^{i}	0.55 ± 0.060^{k}	12.77 ± 0.563^{e}
GD 19	0	16.85 ± 0.330^{f}	$1.96 \pm 0.080^{f,g}$	8.25 ± 0.567^{f}
	0.2	13.16 ± 0.424^{g}	$1.26 \pm 0.075^{i,j}$	11.38 ± 0.516^{e}
	0.4	10.73 ± 0.281^{h}	0.91 ± 0.020^{j}	16.07 ± 0.411^{d}
LD 10	0	20.39 ± 0.659^{e}	2.90 ± 0.046^{d}	11.73 ± 0.769^{e}
	0.2	16.24 ± 0.131^{f}	$2.02 \pm 0.044^{f,g}$	16.37 ± 0.319^{d}
	0.4	13.47 ± 0.268^{g}	$1.73 \pm 0.060^{g,h}$	21.90 ± 0.757^{c}
LD 20	0	27.45 ± 0.744^{c}	4.36 ± 0.194^{b}	17.98 ± 0.400^{d}
	0.2	20.94 ± 0.514^{e}	2.42 ± 0.106^{e}	22.50 ± 0.677^{c}
	0.4	17.73 ± 0.563^{f}	$2.22 \pm 0.093^{e,f}$	32.27 ± 1.408^{b}
LD 30	0	39.40 ± 0.45^{6a}	7.05 ± 0.118^{a}	22.92 ± 1.211^{c}
	0.2	29.47 ± 0.910^{b}	4.39 ± 0.209^{b}	31.37 ± 1.368^{b}
	0.4	22.83 ± 0.786^{d}	3.30 ± 0.270^{c}	40.91 ± 0.364^{a}
ANOVA		$P < 0.001$	$P < 0.001$	$P < 0.001$
LSD 5%		1.537	0.346	2.181
LSD 1%		2.071	0.466	2.938

Data are expressed as mean ± SE. Number of animals in each group is six.
Values which share the same superscript symbols are not significantly different.
ANOVA (*F*-probability) expresses the effect between groups, where $P < 0.001$ is very highly significant.
Where, GD is gestational day, LD is lactation day.

3.2. Developmental and biochemical variables in cerebellum of rat offspring

3.2.1. Effect of both maternal TCDD during perinatal period on monoamines concentrations

The normal values of norepinephrine (NE), epinephrine (E), dopamine (DA) and serotonin (5-HT) were markedly increased in an age-dependent manner in cerebellum of rat offspring to reach maximum values at PND 30 (Table 3). Compared to control offspring, the concentration of these monoamines was gradually decreased (LSD, $P < 0.01$) in both treated groups at all periods except at GD 16 and 19 for both treated groups where a negligible decrease (LSD, $P > 0.05$) was recorded. Minimal values for these monoamines were obtained in both treated groups at PND 30 as compared to control.

3.2.2. Effect of both maternal TCDD during perinatal period on γ-aminobutyric acid (GABA) concentration

The concentration of GABA in cerebellum of control rat offspring exhibited a stepwise increase with the age progress from GD 16 to PND 30. In both treated groups, the concentration of GABA was gradually increased (LSD; $P < 0.01$) during the examined ages except at GD 16 for both treated groups where this elevation was non-significant (LSD; $P > 0.05$) with respect to control group (Table 4). These increases became significant at PND 30 in the 1st and 2nd treated groups with respect to the corresponding control (1.35 and 2.90 vs. 1.02 μg/g, respectively).

3.2.3. Effect of both maternal TCDD during perinatal period on acetylcholinesterase (AchE) activity

The normal values of AchE were gradually increased in an age-dependent manner in cerebellum of offspring and reached maximum values at PND 30 (Table 4). Both maternal administrations of TCDD exacerbated the level of AchE in the cerebellum of offspring and the effect was highly significant (LSD; $P < 0.01$) from GD 16 to PND 30 in comparison with the corresponding control. Notably, this drop continued regularly reaching its lowest level in both treated groups at PND 30.

Generally, for all tested ages, the reduction in T3, T4, GH, monoamines and AchE, and elevation in TSH and GABA were more obvious in high dose group (0.4 μg/kg maternal TCDD) than the low dose group (0.2 μg/kg maternal TCDD) (Tables 1–4). Also, in both dams and offspring, the general effect between groups, for all examined parameters and ages, was very highly significant ($P < 0.001$), as assessed by one-way ANOVA analysis (Tables 1–4).

4. Discussion

The current study shows gradual increases of serum thyroxine (T4), triiodothyronine (T3) and thyrotropin (TSH) levels at

Table 2
Effect of different doses of maternal TCDD in thyroid functions [thyroxine (T4, ng/100 ml), triiodothyronine (T3, ng/100 ml), thyrotropin (TSH, ng/100 ml) and growth hormone (GH, ng/100 ml)] of their offspring during perinatal period.

Periods	TCDD (μg/kg)	Serum T4	Serum T3	Serum TSH	Serum GH
GD16	0	$12.10 \pm 0.098^{e,f}$	$0.47 \pm 0.035^{g-i}$	3.20 ± 0.097^{j}	1.01 ± 0.077^{h}
	0.2	7.94 ± 0.066^{h}	$0.20 \pm 0.067^{h,i}$	$4.75 \pm 0.115^{h,i}$	$0.51 \pm 0.011^{i-k}$
	0.4	4.09 ± 0.165^{j}	0.11 ± 0.089^{i}	6.96 ± 0.207^{g}	0.23 ± 0.024^{k}
GD 19	0	13.73 ± 0.122^{d}	$0.95 \pm 0.080^{e,f}$	$3.91 \pm 0.133^{i,j}$	1.71 ± 0.122^{f}
	0.2	9.19 ± 0.100^{g}	$0.55 \pm 0.051^{g,h}$	7.07 ± 0.227^{g}	0.70 ± 0.042^{i}
	0.4	5.49 ± 0.207^{i}	$0.23 \pm 0.017^{h,i}$	11.14 ± 0.505^{e}	$0.35 \pm 0.067^{j,k}$
PND 10	0	15.72 ± 0.326^{c}	2.61 ± 0.091^{d}	$6.10 \pm 0.395^{g,h}$	3.06 ± 0.155^{d}
	0.2	11.62 ± 0.162^{f}	1.22 ± 0.109^{e}	11.27 ± 0.769^{e}	1.41 ± 0.136^{g}
	0.4	7.86 ± 0.270^{h}	$0.71 \pm 0.046^{f,g}$	16.43 ± 0.742^{c}	$0.42 \pm 0.015^{i-k}$
PND 20	0	17.20 ± 0.153^{b}	4.40 ± 0.214^{b}	8.65 ± 0.478^{f}	4.02 ± 0.085^{b}
	0.2	14.21 ± 0.357^{d}	2.27 ± 0.174^{d}	16.22 ± 0.295^{c}	2.19 ± 0.115^{e}
	0.4	9.37 ± 0.176^{g}	1.26 ± 0.113^{e}	20.79 ± 0.590^{b}	$0.60 \pm 0.013^{i,j}$
PND 30	0	19.83 ± 0.474^{a}	5.61 ± 0.136^{a}	13.01 ± 0.543^{d}	4.83 ± 0.176^{a}
	0.2	17.24 ± 0.706^{b}	3.39 ± 0.223^{c}	19.56 ± 0.594^{b}	3.48 ± 0.120^{c}
	0.4	12.58 ± 0.308^{e}	2.36 ± 0.281^{d}	26.53 ± 1.024^{a}	$1.18 \pm 0.116^{g,h}$
ANOVA		$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
LSD 5%		0.857	0.388	1.501	0.285
LSD 1%		1.154	0.523	2.021	0.384

Data are expressed as mean ± SE. Number of animals in each group is six.
Values which share the same superscript symbols are not significantly different.
ANOVA (*F*-probability) expresses the effect between groups, where $P < 0.001$ is very highly significant.
Where, GD is gestation day, PND is postnatal day.

Table 3
Effect of different doses of maternal TCDD in monoamines (μg/g) of their offspring during perinatal period.

Periods	TCDD (μg/kg)	Norepinephrine (NE)	Epinephrine (E)	Dopamine (DA)	Serotonin (5-HT)
GD16	0	0.05 ± 0.004^{g}	$0.10 \pm 0.006^{d,e}$	$0.10 \pm 0.071^{f,g}$	$0.14 \pm 0.009^{d-f}$
	0.2	0.03 ± 0.002^{g}	$0.05 \pm 0.002^{d,e}$	$0.06 \pm 0.005^{f,g}$	$0.08 \pm 0.003^{e,f}$
	0.4	0.02 ± 0.006^{g}	0.03 ± 0.003^{e}	0.03 ± 0.005^{g}	0.04 ± 0.006^{f}
GD 19	0	$0.10 \pm 0.002^{f,g}$	$0.17 \pm 0.001^{c-e}$	$0.16 \pm 0.004^{d-f}$	$0.20 \pm 0.005^{d-f}$
	0.2	0.05 ± 0.005^{g}	$0.08 \pm 0.004^{d,e}$	$0.11 \pm 0.008^{e-g}$	$0.10 \pm 0.001^{d-f}$
	0.4	0.04 ± 0.004^{g}	$0.06 \pm 0.004^{d,e}$	$0.06 \pm 0.001^{f,g}$	$0.09 \pm 0.001^{d-f}$
PND 10	0	0.43 ± 0.008^{d}	0.31 ± 0.001^{c}	$0.21 \pm 0.010^{d,e}$	0.31 ± 0.001^{d}
	0.2	0.09 ± 0.003^{g}	$0.12 \pm 0.004^{d,e}$	$0.16 \pm 0.009^{d-f}$	$0.17 \pm 0.006^{d-f}$
	0.4	0.07 ± 0.005^{g}	0.09 ± 0.001^{b}	$0.10 \pm 0.004^{e-g}$	$0.12 \pm 0.004^{d-f}$
PND 20	0	0.90 ± 0.044^{b}	0.58 ± 0.004^{b}	0.60 ± 0.109^{b}	1.07 ± 0.113^{b}
	0.2	$0.19 \pm 0.002^{e,f}$	$0.21 \pm 0.001^{c,d}$	0.22 ± 0.001^{d}	$0.28 \pm 0.008^{d,e}$
	0.4	$0.10 \pm 0.004^{f,g}$	$0.13 \pm 0.005^{d,e}$	$0.13 \pm 0.005^{d-f}$	$0.19 \pm 0.004^{d-f}$
PND 30	0	1.28 ± 0.004^{a}	1.06 ± 0.001^{a}	1.70 ± 0.084^{a}	2.27 ± 0.243^{a}
	0.2	0.68 ± 0.006^{c}	0.33 ± 0.001^{c}	0.37 ± 0.003^{c}	$0.93 \pm 0.118^{b,c}$
	0.4	0.24 ± 0.001^{e}	$0.19 \pm 0.005^{c-e}$	0.22 ± 0.001^{d}	0.84 ± 0.062^{c}
ANOVA		$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
LSD 5%		0.092	0.173	0.109	0.224
LSD 1%		0.124	0.233	0.146	0.302

Data are expressed as mean ± SE. Number of animals in each group is six.
Values which share the same superscript symbols are not significantly different.
ANOVA (*F*-probability) expresses the effect between groups, where $P < 0.001$ is very highly significant.
Where, GD is gestational day, PND is postnatal day.

gestation day (GD) 16 and 19, and at lactation day (LD) 10, 20 and 30 in control maternal rat and their offspring. Gärtner (2009) postulated that the demand of thyroid hormones (THs) increases during pregnancy to about 30–50% and the thyroid has to cope with this increase. This state may reflect the higher transfer of THs from pregnant females to their fetuses during pregnancy and/or more efficiency of thyroid gland to produce THs after birth (Jiskra et al., 2007; Ahmed et al., 2008; El-bakry et al., 2010). Moreover, the coordination between TH transporters (the monocarboxylate transporters, organic anion transporting polypeptide and light and heavy-types amino acid transporters) may regulate transplacental TH passage from mother to fetus (Loubière et al., 2010). In addition, the gradual increase of TSH is necessary for the development of thyroid gland during this sensitive period (Ahmed et al., 2010; El-bakry et al., 2010). Thus, it can suggest that normal maternal thyroid functions are required to prevent the appearance of any thyroid disorders during embryonic or fetal periods. Also, in the present study, growth hormone (GH) of control rat offspring was markedly elevated in an age-dependent manner from GD 16 to postnatal day (PND) 30. This hormone is a key factor controlling postnatal growth and development (Zhou et al., 2005; Wong et al., 2006; Ahmed et al., 2010; El-bakry et al., 2010). Generally, hormones of both the hypothalamic-pituitary GH and thyrotropin–thyroid axes are required for normal growth (Wasniewska

Table 4
Effect of different doses of maternal TCDD in γ-aminobutyric acid (GABA, μg/g) and acetylcholinesterase (AchE, U/100 mg) of their offspring during perinatal period.

Periods	TCDD (μg/kg)	GABA	AchE
GD16	0	0.06 ± 0.001^{i}	1.04 ± 0.075^{g}
	0.2	0.18 ± 0.006^{i}	$0.53 \pm 0.004^{h,i}$
	0.4	$0.29 \pm 0.001^{g-i}$	0.26 ± 0.062^{i}
GD 19	0	0.16 ± 0.001^{i}	1.67 ± 0.109^{f}
	0.2	$0.26 \pm 0.001^{h,i}$	1.03 ± 0.051^{g}
	0.4	$0.72 \pm 0.061^{e,f}$	$0.75 \pm 0.057^{g,h}$
PND 10	0	$0.27 \pm 0.002^{h-i}$	2.72 ± 0.115^{d}
	0.2	$0.52 \pm 0.075^{f,g}$	1.39 ± 0.073^{f}
	0.4	1.42 ± 0.094^{c}	1.03 ± 0.033^{g}
PND 20	0	$0.43 \pm 0.003^{g,h}$	3.75 ± 0.091^{b}
	0.2	$0.87 \pm 0.045^{d,e}$	2.19 ± 0.104^{e}
	0.4	1.90 ± 0.048^{b}	1.55 ± 0.091^{f}
PND 30	0	1.02 ± 0.091^{d}	5.04 ± 0.27^{a}
	0.2	1.35 ± 0.06^{c}	3.18 ± 0.183^{c}
	0.4	2.90 ± 0.24^{a}	2.34 ± 0.156^{e}
ANOVA		$P < 0.001$	$P < 0.001$
LSD 5%		0.230	0.344
LSD 1%		0.310	0.464

Data are expressed as mean ± SE. Number of animals in each group is six.
Values which share the same superscript symbols are not significantly different.
ANOVA (*F*-probability) expresses the effect between groups, where $P < 0.001$ is very highly significant.
Where, GD is gestational day, PND is postnatal day.

et al., 2003; El-bakry et al., 2010). My group suggests that the THs may regulate the growth and development, in part, affecting GH function (Ahmed et al., 2010).

On the other hand, during the current experimental period, there was reduction in serum T4 and T3 levels which was accompanied by increase in values of serum TSH of maternal rats and their offspring due to both maternal administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) with respect to control. Concomitantly, TCDD significantly decreased THs levels in dams (Nishimura et al., 2002, 2003) and their offspring (Sauer et al., 1994; Seo et al., 1995; Morse et al., 1996; Kakeyama and Tohyama, 2003). Dioxins affect TH metabolism (ten Tusscher and Koppe, 2004; Turyk et al., 2007; Ottinger et al., 2008) via aryl hydrocarbon receptor (AhR) (Nishijo et al., 2007; Miyazaki et al., 2008). Also, dioxins cause hypothyroidism during perinatal (Nishimura et al., 2003, 2005) and adult life (Boas et al. 2006) by inducing the uridine diphosphoglucuronosyl transferase (UDPGT), a thyroid hormone metabolizing enzyme, in liver to accelerate the elimination of T4 (Brouwer et al., 1998; Viluksela et al., 2004). Thus, it can be inferred from the above mentioned results that thyroid function abnormalities in pregnancy can result in maternal and neonatal hypothyroidism. Also, in the current study, serum GH level was markedly decreased in both treated groups from GD 16 to PND 30 if compared to control group. This observation is supported by Koopman-Esseboom et al. (1994), Sauer et al. (1994) and Kobayashi et al. (2009) who postulated that dioxins may affect growth and development through thyroid impairment in mother–infant. Clements et al. (2009) reported that TCDD may induce a variety of effects by modifying hypothalamic structures that play a role in growth and reproductive development. Interestingly, even minor changes in maternal TH levels during pregnancy may impair the infant's development (Pop et al., 1999). These studies imply that TCDD levels may influence the maternal and fetal hypothalamic-pituitary-thyroid system.

Because the balance between excitation and inhibition is essential for the normal function and development of cerebellum, the changes in monoamines, γ-aminobutyric acid (GABA) and acetylcholinesterase (AchE) due to THs will determine the efficacy of these pathways in this region. The concentrations of monoamines [norepinephrine (NE), epinephrine (E), dopamine (DA) and serotonin (5-HT)] and γ-aminobutyric acid (GABA) and the activity of acetylcholinesterase (AchE) were gradually increased in cerebellum of control rat offspring from GD 16 to PND 30. Previously, my group recorded that monoamines (NE, E, DA and 5-HT) and GABA contents, and AchE activities were significantly and gradually increased with the age from PND 7 to 21 in cerebellum of rat offspring (Ahmed et al., 2010). In general, the monoaminergic, GABA-ergic or cholinergic systems are essential for normal brain development as a modulator of neuronal proliferation, migration and differentiation processes (Ahmed, 2004; Coccini et al., 2007; Ahmed et al., 2007a, 2010). Also, TH has been shown to regulate several neurotransmitter systems, including the development of monoaminergic (Aszalós, 2007; Ahmed et al., 2008), GABA-ergic (Wiens and Trudeau, 2006; Aszalós, 2007; Ahmed et al., 2008) and cholinergic transmission in various brain regions of rat (Evans et al., 1999). It is possible that the elevation in the previous parameters, in the current experiment, is synergistic and closely interrelated with the behavior of THs during the experimental period. This synergistic mechanism is required for the developing cerebellum.

A non-appreciable decrease was observed in the concentration of NE, E, DA and 5-HT during the prenatal period (GD 16 and 19) while these decline became well demonstrated during the postnatal period (PND 10, 20 and 30) in cerebellum of rat offspring in both treated groups if compared to their respective control. Similarly, in utero and lactation, TCDD exposure decreases the 5-HT (Bjerke et al., 1994; Kuchiiwa et al., 2002) and DA levels in the CNS (Bjerke et al., 1994). Perinatal exposure of rats to dioxins has been shown to induce effects on brain DA concentrations (Seegal, 1992) and TH status (Huisman et al., 1995; Tanida et al., 2009), and these changes do not recover until sexual maturation (Tanida et al., 2009). This implies that TCDD contributes to the incidence of developmental neuroendocrine disorders. Also, these alterations are similar to those seen in different brain regions of hypothyroid rats where the impairment in development of monoaminergic system was reported by several investigators and my group (Vaccari et al., 1990; Ahmed et al., 2008; Ahmed, 2009). Moreover, the PCBs reduce DA levels in vitro and in vivo (Hany et al., 1999) and display estrogens, androgens, and corticosteroids changes (Rice, 1999), which may affect brain development (Hany et al., 1999). In many species, including humans, perinatal exposure to dioxin and PCB congeners can produce neurologic impairment due to these toxicants could alter production of proteins such as coactivators or corepressors that regulate transcription of TH-regulated genes (Porterfield, 2000). From the correlation between the previous observations and the present experiment, it seems logic to infer that both maternal TCDD may induce perinatal hypothyroidism in offspring and may alter the monoaminergic system indirectly through the hormonal imbalance.

In the current experiment, the increase in the concentration of GABA was highly significant from GD 19 to PND 30 while this elevation was non-substantial at GD 16 only in cerebellum of rat offspring in both treated groups with respect to control. TCDD-treated males had significantly higher numbers of GABA/Glu neurons than controls (Krishnan and Petersen, 2004; Petersen et al., 2006). The increase of GABA concentration was recorded in rat cerebellum after exposure to polychlorinated naphthalenes which was similar to TCDD (Vinitskaya et al., 2005). Developmental exposure to PCB52 increases extracellular GABA in cerebellum, thus contributing to motor coordination impairment (Boix et al., 2010). At variance with the above evidences, Matsumoto et al. (2010) demonstrated that a number of fetal hypothalamic components, including glutamine and GABA, are reduced by TCDD. A more logical reason for this discrepancy in GABA level is the secondary

effects of THs and the complex structure of the brain in different experimental animals. Perhaps THs inhibit GABA transporter synthesis, thus lower TH levels resulted in an increased number of transporters in neuron membranes and therefore greater GABA uptake by brain homogenates (Ahmed et al., 2008). This means that disruption of the TH axis can cause hypothyroidism (Ahmed et al., 2010), mental retardation and neurological defects (Jugan et al., 2010). These several pathways may mediate via AhR during the development of CNS (Hays et al., 2002) and may due to the toxicants (TCDD) could be either agonists or antagonists for TH receptor binding (Porterfield, 2000). Also, prenatal exposure to PCBs with TH-disrupting potencies leads to abnormal brain development via perturbations on the mRNA expression of genes involved in glutamatergic neurotransmission (Takahashia et al., 2009). Thus, these data may indicate that both maternal TCDD may disturb GABA signaling in a cerebellum during the perinatal period and induce the neurodevelopmental toxicity via mother–offspring thyroid axis.

The baseline level of AchE in cerebellum of rat offspring was decreased in both treated groups below normal level from GD 16 to LD 30. The administration in the course of development (pre- or post-natal periods) of different types of PCBs depressed the choline acetyltransferase (ChAT) activity in different brain regions (Donahue et al., 2004; Coccini et al., 2007). Alterations of the thyroid state can affect the maturation of neurochemical endpoints, including AchE activity (Coccini et al., 2007; Cromwell et al., 2007). A reduction in T4 due to exposure to PCB may be responsible for the alterations in the cholinergic system because hypothyroidism leads to lowered expression of ChAT (Dufault et al., 2005). These alterations can mediate via AhR and related factors which are expressed in various regions of CNS during the development (Williamson et al., 2005). These observations strengthen the possibility that the maternal administration of TCDD affects the development of cholinergic system, which may be mediated by the thyroid system.

Overall, the present work showed that the toxicity of TCDD was dose and age dependent. If dioxins functionally decrease THs in the mother during pregnancy, or in the fetus or neonate during critical periods of neurological development (TH-dependent brain development), permanent brain damage is likely to result (Porterfield, 1994, 2000; Petersen et al., 2006; Tanida et al., 2009). Even more interesting are the elegant studies discussed by Koibuchi (2006), Dickerson et al. (2009) and Jugan et al. (2010) who reported that when animals are exposed to polyhalogenated aromatic hydrocarbons, they exhibit neurological abnormalities similar to those seen in cretinism both in humans and animals.

In conclusion, both maternal administrations of TCDD may impair the development of cerebellum of their offspring via THs and this may, in general, delay the growth and differentiation of the neuroendocrine system (Fig. 1). Thus, TCDD may act as endocrine- and neural-disrupting actions on the development of THs-cerebellum axis during perinatal period. However, it remains to be clarified whether the reported effects of TCDD on development of neuroendocrine system in animal models might be relevant to human health.

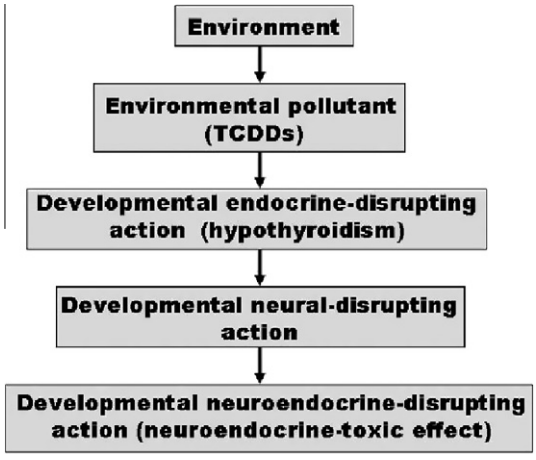

Fig. 1. Schematic diagram for the toxicology of TCDD on the developmental neuroendocrine system.

5. Future directions

There are still many uncertainties on the effect of endocrine disrupting chemicals on thyroid hormones-dependent brain development. Thus, it is critical that neuroendocrinologists and neurotoxicologists work together to fully characterize the multiple neuro-molecular mechanisms of TCDD, particularly the aryl hydrocarbon receptors. Also, more information is needed to determine the role of growth factors and some antioxidant compounds against the neurotoxic effect of persistent organic pollutants, particularly TCDD during the development.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.fct.2011.03.008.

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