Prenatal Aroclor 1254 Exposure Selectively Alters Regional Glial Fibrillary Acidic Protein Levels in the Rat Brain

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ABSTRACT

In this study we investigated the effects of prenatal Aroclor 1254 administration on the development of the astrocyte marker glial fibrillary acidic protein (GFAP) in discrete brain regions of the progeny. Ninety days after birth GFAP concentrations were significantly lower in the brainstem and striatum of male and female offspring while GFAP levels were increased in the cerebellum of male offspring exposed prenatally to Aroclor 1254.

INTRODUCTION

Polychlorinated biphenyls (PCBs) are well-known developmental neurotoxins although the mechanism involved is unresolved[1]. In adult rats and macaques retention of ortho-substituted PCBs in the brain is associated with decreased striatal dopamine levels, presumably by the direct inhibition of tyrosine hydroxylase by ortho-substituted PCBs[2]. However, perinatal Aroclor 1016 administration results in increased striatal dopamine levels in the rat[3]. PCBs may also have an indirect effect on brain development by decreasing circulating thyroxine (T4) levels, a hormone essential in normal brain development[4]. It has been previously shown that perinatal PCB exposure results in decreased plasma thyroid hormones and increased cerebral metabolism of T4 in fetal[5] and neonatal rats[6].
The effects of perinatal hypothyroidism are most acute in the cerebellum, resulting in increased neuronal cell death and an inhibition of neuronal maturation and as a response the hypertrophy of astrocytes (termed astrogliosis)[7]. Astrogliosis can be easily detected by measuring increases in glial fibrillary acidic protein (GFAP) levels, the major component of intermediary filaments in mature astrocytes[8].
In the present study we investigated the effects of prenatal exposure to polychlorinated biphenyls on the levels of GFAP in brain regions of neonatal rats and adult offspring.

MATERIAL AND METHODS

Pregnant Wistar WU rats received oral doses of 5 or 25 mg Aroclor 1254 per kg body weight (dissolved in cornoil, 2 ml/kg bodyweight) on day 10 to 16 of gestation, or the vehicle alone. Four days after birth nests were reduced to 4 males and 4 females. On 21 and 90 days postpartum, offspring (N= 8 to 10 litters per treatment) were sacrificed by decapitation and brain regions (cerebellum, brainstem, hippocampus and striatum) were dissected, weighed and stored at -80 °C untill analysis. GFAP levels were measured in homogenates of the brain regions using a sandwich ELISA[9]. Protein levels were determined with the bicinchoninic acid protein assay from Pierce.

RESULTS

GFAP levels in homogenates of the cerebellum, brainstem, hippocampus and striatum of the offspring of pregnant rats exposed to Aroclor 1254 are presented in Table 1. Twenty one days after birth GFAP levels were significantly elevated (+25%) relative to controls in cerebellar homogenates from female and male offspring from pregnant rats treated with 25 mg Aroclor 1254 per kg bw. Within dose groups cerebellar GFAP levels increased significantly from day 21 to day 90, and male offspring exhibited higher GFAP levels compared to female offspring at both time points. On day 90 postpartum GFAP levels were significantly increased in only male offspring from the high dose group (125% of control levels). Brainstem GFAP concentrations increased from day 21 to day 90 in both male and female offspring from the control group, however this increase was absent in offspring from both PCB treatment groups, leading to significantly lower GFAP levels relative to controls. A less dramatic increase in striatal GFAP levels was observed between 21 and 90 days after birth in control groups, while male and female offspring from the 25 mg/kg bw group exhibited no increase in GFAP concentrations. No effect was observed on GFAP concentrations in the hippocampus of rats from PCB-treated dams at either time point. There were no obvious sex related differences in GFAP expression in the brainstem, hippocampus or striatum of the offspring.

DISCUSSION

The results demonstrate that the treatment of pregnant rats with Aroclor 1254 results in long term alterations of GFAP concentrations in the brainstem (5 and 25 mg/kg) and striatum (25 mg/kg) of both male and female offspring. In the prenatally Aroclor 1254 exposed animals GFAP concentrations in the striatum and brainstem no longer increase after postnatal day 21, which suggests that astrocyte maturation is inhibited. A disruption of cellular organisation in the brainstem has potential consequences for the ascending dopaminergic system, and could explain effects observed in GFAP and dopamine concentrations in the striatum.

Directly neurotoxic substances, such as kainic acid, induce astrogliosis, which can be

quantified as permanently increased GFAP concentrations in the hippocampus and striatum, respectively[8]. Since we observed no increases in hippocampal or striatal GFAP concentrations on 21 days after birth, it appears that Aroclor 1254 does not induce excess neuronal cell death in these brain regions.

The increase of GFAP levels in the cerebella of neonatal and adult male offspring after maternal PCB treatment resembles the effects of perinatal hypothyroidism induced by maternal treatment with propylthiouracil (PTU)[7]. In the cerebellum, perinatal hypothyroi

TABLE 1

GFAP concentrations (μg/mg protein) in brain regions of rats exposed prenatally to Aroclor 1254

		Aroclor 1254 (mg/kg bw)		
		0	5	25
cerebellum				
♂	21[a]	0.98±0.05	1.09±0.05	1.25±0.13[b]
	90	3.38±0.21	3.59±0.16	4.31±0.25[b]
♀	21	0.77±0.05	0.89±0.07	1.02±0.06[b]
	90	2.14±0.06	2.18±0.14	2.22±0.16
brainstem				
♂	21	2.02±0.09	1.95±0.08	1.80±0.10
	90	3.25±0.32	1.83±0.07[b]	1.93±0.09[b]
♀	21	2.24±0.19	1.71±0.10[b]	1.87±0.17
	90	2.72±0.22	1.89±0.11[b]	1.93±0.13[b]
hippocampus				
♂	21	1.83±0.23	1.69±0.30	1.72±0.32
	90	1.29±0.09	1.39±0.11	1.39±0.13
♀	21	1.58±0.16	1.52±0.11	1.62±0.17
	90	1.21±0.08	1.12±0.16	1.42±0.23
striatum				
♂	21	0.57±0.04	0.46±0.04	0.63±0.09
	90	0.74±0.05	0.64±0.04	0.59±0.04[b]
♀	21	0.52±0.04	0.56±0.07	0.50±0.06
	90	0.81±0.09	0.71±0.04	0.54±0.05[b]

[a]day after birth, [b]significantly different from controls, $P<0.05$

dism leads to increased neuronal cell death and decreased dendritic outgrowth which stimulates astrogiosis[7].

In summary, prenatal exposure of the rat to Aroclor 1254 induces a differential astroglial response in discrete brain regions of young adult rats, which may in part be caused by PCB-induced perinatal hypothyroidism.

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