Toxicology 325 (2014) 200–208

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Bisphenol-A exposures and behavioural aberrations: Median and linear spline and meta-regression analyses of 12 toxicity studies in rodents

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ARTICLE INFO

Article history:
Received 17 July 2014
Received in revised form 5 September 2014
Accepted 16 September 2014
Available online 19 September 2014

Keywords:
Bisphenol-A
Rodents
Developmental exposures
Median and linear spline and meta-regression

ABSTRACT

Exposures to bisphenol-A, a weak estrogenic chemical, largely used for the production of plastic containers, can affect the rodent behaviour. Thus, we examined the relationships between bisphenol-A and the anxiety-like behaviour, spatial skills, and aggressiveness, in 12 toxicity studies of rodent offspring from females orally exposed to bisphenol-A, while pregnant and/or lactating, by median and linear splines analyses. Subsequently, the meta-regression analysis was applied to quantify the behavioural changes. U-shaped, inverted U-shaped and J-shaped dose–response curves were found to describe the relationships between bisphenol-A with the behavioural outcomes. The occurrence of anxiogenic-like effects and spatial skill changes displayed U-shaped and inverted U-shaped curves, respectively, providing examples of effects that are observed at low-doses. Conversely, a J-dose–response relationship was observed for aggressiveness. When the proportion of rodents expressing certain traits or the time that they employed to manifest an attitude was analysed, the meta-regression indicated that a borderline significant increment of anxiogenic-like effects was present at low-doses regardless of sexes (β) = −0.8%, 95% C.I. −1.7/0.1, P = 0.076, at ≤120 μg bisphenol-A. Whereas, only bisphenol-A-males exhibited a significant inhibition of spatial skills (β) = 0.7%, 95% C.I. 0.2/1.2, P = 0.004, at ≤100 μg/day. A significant increment of aggressiveness was observed in both the sexes (β) = 67.9, C.I. 3.4, 172.5, P = 0.038, at >4.0 μg. Then, bisphenol-A treatments significantly abrogated spatial learning and ability in males ($P < 0.001$ vs. females). Overall, our study showed that developmental exposures to low-doses of bisphenol-A, e.g. ≤120 μg/day, were associated to behavioural aberrations in offspring.

1. Introduction

It is noteworthy that the reproductive endocrine system is sexually dimorphic, accommodating common sex differences in gametogenesis, steroidgenesis, and the sexual behaviour. The control of these processes takes place in the hypothalamic-limbic neural network, that is governed in a sex-specific manner by the sexual hormones, including estradiol, progesterone, testosterone and dihydrotestosterone, during critical periods of development, such as late in the fetal development and soon after birth in mammals. This complex system develops in a sexually dimorphic manner and results in the typical reproductive physiology and the sexual behaviour in adulthood. In males, testosterone is required to establish and maintain neural circuits that later control the male-typical behaviour (Lenz and McCarthy, 2010). To induce masculinization is also necessary the synthesis, in the developing brain, of aromatase enzyme for the conversion of testosterone to estradiol and its interaction upon neural estrogen receptors, ERα and ERβ, (Cornil et al., 2006; Juntti et al., 2010). Conversely, female fetal brain has decreased exposures to testosterone and estradiol (Lenz and McCarthy, 2010). In females, brain is even protected by the circulating α-fetoprotein from masculinization and defeminisation by estrogens (Bakker et al., 2006).

Endocrine-disrupting chemicals are synthetic and/or naturally occurring compounds released in the environment, that can interfere with the endocrine system (Diamanti-Kandarakis et al., 2009). Certain endocrine disruptors are compounds that mimic or inhibit the actions of endogenous hormones, and cause reproductive dysfunctions and behavioural aberrations (Diamanti-Kandarakis et al., 2009). Among the endocrine-disrupting chemicals, there is the carbon-based synthetic compound bisphenol-A (BPA; CAS# 80-05-7) or 4,4′-(propane-2,2-diyl) diphenol [$(CH_3)_2C(C_6H_4OH)_2$], a weak estrogenic chemical with mixed estrogen agonist and antagonist properties (Kundakovic and Champagne, 2011), largely used in the production of plastic food containers, receipts, and dental sealants (Vandenberg et al., 2007). This endocrine disruptor

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http://dx.doi.org/10.1016/j.tox.2014.09.008
0300-483X/

Table 1
Description of the 12 toxicity studies of rodent offspring from females orally exposed to bisphenol-A, while pregnant and/or lactating, that were included in the median and linear spline and meta-regression analyses.

Species	Oral treatment and feeding	Exposure dose	PNDs[a]	N	Female		N	Males		Bibliography
Variations in percentage (%) or time (sec) that animal employed to express an attitude										
Exploratory and anxiety-like behaviour										
Wistar rats	Controls		28	24	23 s/5 min	Ref	24	25 s/5 min	Ref	(Fujimoto, 2006)
	0.015 mg/kg bw (gest.)	5 μg/day	28	24	17 s/5 min		24	15 s/5 min		
CD-1 mice	Controls		70	14	10 s/5 min	Ref	14	20 s/5 min	Ref	(Gioiosa et al., 2007)
	0.01 mg/kg bw (gest./lact.)	0.4 μg/day	70	14	11 s/5 min		14	20 s/5 min		
C57BL/6J mice	Controls		20	9	40 s/10 min	Ref	7	40 s/10 min	Ref	(Cox et al., 2010)
	50 mg/kg fw (gest.)	200 μg/day	20	9	45 s/10 min		7	25 s/10 min		
	Controls		70–77	4	40 s/10 min	Ref	5	200 s/10 min	Ref	
	50 mg/kg fw (gest.)	200 μg/day	70–77	5	35 s/10 min		13	150 s/10 min		
Peromyscus Maniculatus mice	Controls		74	13	125 s/5 min	Ref	20	210 s/5 min	Ref	(Jasarevic et al., 2011)
	50 mg/kg fw (gest.)	200 μg/day	74	10	70 s/5 min		19	50 s/5 min		
C57BL/6J mice	Controls		22	13	80 s/10 min	Ref	15	79 s/10 min	Ref	(Wolstenholme et al., 2011)
	1.25 mg/kg fw (gest.)	5 μg/day	22	18	78 s/10 min		21	75 s/10 min		
	Controls		22	10	63 s/10 min	Ref	12	76 s/10 min	Ref	(Wolstenholme et al., 2012)
	5 mg/kg fw (gest.)	20 μg/day	22	11	64 s/10 min		18	77 s/10 min		
Wistar rats	Controls		60–70	8	60 s/5 min	Ref	15	15 s/5 min	Ref	(Patisaul et al., 2012)
	1 mg/liter water (gest./lact.)	72 μg/day	60–70	25	40 s/5 min		12	30 s/5 min		
ICR mice	Controls		59	10	11 s/5 min	Ref	10	5 s/5 min	Ref	(Xu et al., 2012)
	0.4 mg/kg bw (gest.)	12 μg/day	59	10	5 s/5 min		10	4 s/5 min		
	4 mg/kg bw (gest.)	120 μg/day	59	10	6 s/5 min		10	2 s/5 min		
	Controls		59	10	11 s/5 min	Ref	10	7 s/5 min	Ref	
	0.4 mg/kg bw (lact.)	12 μg/day	59	10	5 s/5 min		10	5 s/5 min		
	4 mg/kg bw (lact.)	120 μg/day	59	10	10 s/5 min		10	3 s/5 min		
Peromyscus Maniculatus mice	Controls		67	11	150 s/5 min	Ref	8	210 s/5 min	Ref	(Jasarevic et al., 2013)
	0.05 mg/kg fw (gest.)	0.2 μg/day	67	6	140 s/5 min		6	160 s/5 min		
	5 mg/kg fw (gest.)	20 μg/day	67	7	80 s/5 min		10	90 s/5 min		
	50 mg/kg fw (gest.)	200 μg/day	67	9	90 s/5 min		8	70 s/5 min		
BALB/c mice	Control		60	10	60 s/10 min	Ref	8	20 s/10 min	Ref	(Kundakovic et al., 2013)
	0.002 mg/kg bw (gest.)	0.06 μg/day	60	12	40 s/10 min		10	30 s/10 min		
	0.02 mg/kg bw (gest.)	0.6 μg/day	60	10	30 s/10 min		10	40 s/10 min		
	0.2 mg/kg bw (gest.)	6 μg/day	60	12	20 s/10 min		12	50 s/10 min		
Spatial learning and ability behaviour										
Peromyscus Maniculatus mice	Controls (1° day/training)		60	13	210 s/300 s	Ref	20	120/300 s	Ref	(Jasarevic et al., 2011)
	50 mg/kg fw (gest.)	200 μg/day	60	10	180 s/300 s		19	170/300 s		
	Controls (2° day/training)		60	13	150 s/300 s	Ref	20	50 s/300 s	Ref	
	50 mg/kg fw (gest.)	200 μg/day	60	10	80 s/300 s		19	130 s/300 s		
	Controls (3° day/training)		60	13	200 s/300 s	Ref	20	40 s/300 s	Ref	
	50 mg/kg fw (gest.)	200 μg/day	60	10	150 s/300 s		19	140 s/300 s		
	Controls (4° day/training)		60	13	280 s/300 s	Ref	20	40 s/300 s	Ref	
	50 mg/kg fw (gest.)	200 μg/day	60	10	200 s/300 s		19	160 s/300 s		
	Controls (5° day/training)		60	13	250 s/300 s	Ref	20	40 s/300 s	Ref	
	50 mg/kg fw (gest.)	200 μg/day	60	10	190 s/300 s		19	150 s/300 s		
	Controls (6° day/training)		60	13	240 s/300 s	Ref	20	40 s/300 s	Ref	
	50 mg/kg fw (gest.)	200 μg/day	60	10	240 s/300 s		19	150 s/300 s		
	Controls (7° day/training)		60	13	260 s/300 s	Ref	20	30 s/300 s	Ref	
	50 mg/kg fw (gest.)	200 μg/day	60	10	240 s/300 s		19	160 s/300 s		
Peromyscus Maniculatus mice	Controls (1° day/training)		60	11	130 s/300 s	Ref	8	100 s/300 s	Ref	(Jasarevic et al., 2013)
	0.05 mg/kg fw (gest.)	0.2 μg/day	60	6	130 s/300 s		6	140 s/300 s		
	5 mg/kg fw (gest.)	20 μg/day	60	7	90 s/300 s		10	160 s/300 s		
	500 mg/kg fw (gest.)	200 μg/day	60	9	180 s/300 s		8	160 s/300 s		
	Controls (2° day/training)		60	11	60 s/300 s	Ref	8	60 s/300 s	Ref	
	0.05 mg/kg fw (gest.)	0.2 μg/day	60	6	70 s/300 s		6	70 s/300 s		
	5 mg/kg fw (gest.)	20 μg/day	60	7	30 s/300 s		10	80 s/300 s		
	500 mg/kg fw (gest.)	200 μg/day	60	9	60 s/300 s		8	90 s/300 s		
	Controls (3° day/training)		60	11	70 s/300 s	Ref	8	40 s/300 s	Ref	
	0.05 mg/kg fw (gest.)	0.2 μg/day	60	6	70 s/300 s		6	60 s/300 s		
	5 mg/kg fw (gest.)	20 μg/day	60	7	40 s/300 s		10	70 s/300 s		
	500 mg/kg fw (gest.)	200 μg/day	60	9	60 s/300 s		8	100 s/300 s		
	Controls (4° day/training)		60	11	90 s/300 s	Ref	8	30 s/300 s	Ref	
	0.05 mg/kg fw (gest.)	0.2 μg/day	60	6	60 s/300 s		6	60 s/300 s		
	5 mg/kg fw (gest.)	20 μg/day	60	6	40 s/300 s		10	60 s/300 s		
	500 mg/kg fw (gest.)	200 μg/day	60	6	80 s/300 s		8	80 s/300 s		
	Controls (5° day/training)		60	11	80 s/300 s	Ref	8	20 s/300 s	Ref	
	0.05 mg/kg fw (gest.)	0.2 μg/day	60	7	70 s/300 s		6	60 s/300 s		
	5 mg/kg fw (gest.)	20 μg/day	60	7	60 s/300 s		10	90 s/300 s		
	500 mg/kg fw (gest.)	200 μg/day	60	7	70 s/300 s		8	80 s/300 s		
	Controls (6° day/training)		60	11	60 s/300 s	Ref	8	20 s/300 s	Ref	
	0.05 mg/kg fw (gest.)	0.2 μg/day	60	7	60 s/300 s		6	30 s/300 s		
	5 mg/kg fw (gest.)	20 μg/day	60	7	50 s/300 s		10	80 s/300 s		
	500 mg/kg fw (gest.)	200 μg/day	60	7	50 s/300 s		8	70 s/300 s		
	Controls (7° day/training)		60	11	50 s/300 s	Ref	8	20 s/300 s	Ref	
	0.05 mg/kg fw (gest.)	0.2 μg/day	60	7	60 s/300 s		6	30 s/300 s		