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D-Amphetamine-related reinforcing effects are reduced in mice exposed prenatally to estrogenic endocrine disruptors

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Abstract

Estrogenic endocrine disruptors are hormonally active compounds that can bind to estradiol receptors. Central dopamine pathways have been reported to be affected by early developmental exposure to estrogenic endocrine disruptors. In the present study, pregnant female CD-1 mice were allowed to drink spontaneously either oil or environmentally relevant low doses of two estrogenic compounds, methoxychlor (20 μg/kg) or bisphenol-A (10 μg/kg) during gestation days 11–18. Their adult offspring were assessed for conditioned place preference produced by D-amphetamine (0, 1 or 2 mg/kg). Interestingly, prenatal treatment effects were sex-dependent and no changes in conditioned place preference emerged for the male offspring. Conversely, a clear-cut profile of D-amphetamine-induced conditioned place preference was only shown by oil-exposed females, whereas exposure to bisphenol-A or methoxychlor resulted in little or no place conditioning. Locomotor effects of acute D-amphetamine were not affected by prenatal exposure to bisphenol-A or methoxychlor. As a whole, prenatal exposure to estrogenic endocrine disruptors affected some steps in the organization of the brain dopaminergic systems in the female offspring, thus leading to long-term alterations in neurobehavioral function. These data confirm that exposure to weak environmental estrogens in the period of brain sexual differentiation can influence adult behavior.

Keywords: Prenatal exposure; Brain development; Bisphenol-A; Methoxychlor; D-Amphetamine; Conditioned place preference; Mice

1. Introduction

There is increasing concern about the negative impact on public health of environmental chemicals with estrogenic activity [15,28]. Exposure to chemicals during early development often inflicts toxic consequences that can be qualitatively different from effects on mature nervous systems. The developmental effects of steroids are typically irreversible and are referred to as "organisational", while effects in adults are typically reversible and are referred to as "activational" [5,62]. The ability of estrogenic hormones to affect sexual differentiation of the brain during critical developmental periods is well known [6,31]. Specifically, estrogens or aromatizable androgens play a significant role in regulating neuronal development and formation of neural circuits during the perinatal period. In certain brain regions, these organizational actions of sex steroids can induce permanent sexual dimorphism in synaptic formation, dendritic length, distribution patterns of serotoninergic fibers, and in neuronal connectivity [41]. In addition to reproductive and sexual behavior, a variety of behavioral patterns are organized and sexually differentiated in rodents under the influence of gonadal hormones [8,42,44].

Early events, such as small perturbations of hormonal milieu, have been found to alter ontogenetic pathways and to produce marked effects on brain function and behavior later in life (for a review, see [12,39]). In addition, an early-occurring damage may reveal itself and emerge only after a prolonged latency (e.g. during adulthood or as late as senescence). A growing literature has reported that manmade endocrine-disrupting chemicals may alter development, leading to altered behavior and reproductive capacity in the wildlife [19,20]. Because they represent the end-point of the integrated activity of several neural systems, behavioral indices

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may be particularly sensitive to hormonal perturbation, and even subtle alterations in any component system are likely to be reflected in the disruption or modification of the final behavioral output [50].

Bisphenol-A (BPA) is a widespread estrogenic chemical, which is potentially ingested by humans, being released by polycarbonate plastics, the lining of food cans, and dental sealants [14,47]. BPA has a weak estrogenic activity in vitro and in vivo [35,57], and interacts with the estrogen receptor alpha (ERα) in a unique manner, somewhat different from estradiol [26]. Prenatal exposure to BPA is able to affect the development and function of reproductive organs, as well as adult sexual behavior, especially in the male offspring [7,24,54,60,61,63,64], but also in females [29]. Perinatal exposure to BPA has also been implicated in altered profiles of non-social behaviors, resulting in a reduced motivation to explore and an altered profile of impulsivity in the offspring of rats [1,24].

Methoxychlor (MXC) is used as an insecticide for pets, gardens, crops and livestock. MXC has estrogenic effects only in vivo after demethylation in the liver. In addition, MXC has been reported to bind to androgen receptors and also acts as an anti-androgen [27]. Exposure to MXC during development leads to changes in the reproductive system and behavior in rats and mice [52]. Recent advances have also shown that estrogens interact with the dopaminergic [2,10,23,30,45] and the serotonergic [48] brain systems. Exposure during ontogenetic critical periods to estrogenic pollutants could hence result in an altered development of these major neurochemical pathways (see e.g. [18,40]), thus leading to permanent neurobehavioral alterations in the offspring.

In the present work, we studied the effects of maternal exposure to BPA and MXC, during the last gestational week in mice. These two compounds were administered at low doses, which are environmentally relevant, within the range of human exposure and not teratogenic [14,47] and have been demonstrated to affect behavioral development in previous experiments [51,52]. We assessed in adult animals the possibility that prenatal exposure to BPA or to MXC may influence the development of brain dopaminergic systems. In particular, we investigated potential changes in the reinforcing effects of amphetamine, using a widely validated paradigm, the conditioned place preference (CPP). This paradigm provides a measure of incentive memory of rewarding drug effects, which do impinge on drug action within mesolimbic dopamine systems [53,65]. The specificity of the developmental changes affecting a central neurochemical system can be evaluated by assessing the effects of a psychoactive agent targeting a given system upon the behavioral responses known to be modulated by that system. For this reason, it seemed appropriate to evaluate the behavioral effects that follow amphetamine administration [33], since it is well known that release of dopamine within the dorsal and ventral striatum is involved in such a behavioral change [56]. To the purpose of the present study, a potential alteration in the behavioral effects of amphetamine administration was considered as an index of BPA- and/or MXC-induced long-term effects on the dopaminergic function of the brain.

2. Material and methods

The experimental protocols were approved by the competent institutional authorities and are in close agreement with European Community Directives and with the Italian Law. All efforts were made to minimize animal suffering, to reduce the number of animals used, and to use alternatives to in vivo testing.

2.1. Maternal treatment and procedure

Female CD-1 mice (*Mus musculus domesticus*, Charles River, Calco, Italy) were time-mated and group-housed until starting of treatment. Starting from day 6 after detection of vaginal plug, the females were trained to spontaneously drink a small volume (50 μl) of corn oil purified from tocoferole (Sigma, Milan, Italy) from a modified syringe (without the needle and with a larger hole) introduced in through the cage top every day, 6 h after light onset. All females easily learned to drink the oil as soon as the syringe was introduced in the cage. This procedure allows accurate administration of chemicals without the stress associated with gavage or injection [51,52]. On gestation day 11, each female was individually housed and randomly assigned to one of the following treatment groups (10–12 females per group): oil control, BPA (10 μg of BPA per kg body weight per day) or MXC (20 μg of MXC per kg body weight per day). From gestation day 11–18, each female drank 0.1 ml of corn oil per 50 g body weight per day, with or without the chemicals. Within 12 h following parturition (on gestation day 19), each litter was culled to 10 pups (5 ± 1 males and 5 ± 1 females), which were returned to their biological mothers. On postnatal day 25, offspring were weaned and mice were group-housed with same sex littermates till the moment they were used for testing. At adulthood (60-day old), three males and three females from each litter underwent the CPP test, being assigned to different treatment levels.

2.2. Apparatus

The experimental apparatus consisted of an opaque Plexiglas rectangular box with smooth walls, subdivided into three compartments. The connecting doors between the three compartments could be closed by means of temporary partitions (see [37]). Two cues, one visual and one tactile, were associated with each of the two end-compartments (20 cm × 14 cm × 27 cm each). One compartment was white and had a wide-mesh floor (wire diameter 0.7 mm, mesh width 6 mm), whereas the other one was black and had a narrow mesh floor (wire of 0.2 mm diameter, mesh width 1 mm). The middle compartment had grey walls and a smooth floor. Each compartment was equipped with four infrared

photo-beams, placed on the wall (2 cm above floor). Photocell interruptions were recorded by an IBM computer, equipped with a custom-made software. The apparatus was cleaned after each animal was tested. The following measures were obtained automatically: (1) *time* spent in each compartment; and (2) *activity rate* in each compartment (number of beam interruptions per second). The whole session was automatically subdivided into 5-min intervals. The whole experimental schedule took a total of 6 days, each subject from all three prenatal treatment groups being tested between 10 a.m. and 18 p.m. Testing of different experimental groups was counterbalanced across time. The test was carried out under dim illumination.

2.3. Drugs

D-Amphetamine (AMPH) sulfate was dissolved in saline (SAL, NaCl 0.9%) and injected i.p. in a volume of 1 ml/100 g body weight. AMPH doses were chosen in the range of those used in previous studies (see [38]). Doses are expressed as salt weight.

2.4. Place-conditioning paradigm

The white compartment of the apparatus was drug-paired (i.e. the paired chamber), whereas the black one was SAL-paired (i.e. the unpaired chamber). This "biased" procedure is often reported in the literature on place conditioning (see e.g. [38]). According to a split-litter design, one male and one female from each litter were randomly assigned to be conditioned with one of the three AMPH doses (0, 1 or 2 mg/kg i.p.).

Day 0: Familiarization. Animals were allowed to freely explore the whole apparatus for 10-min session, in a drug-free state.

Days 1 and 3: Animals were injected with the appropriate AMPH dose and immediately placed in the paired chamber of the apparatus for a 20-min session.

Days 2 and 4: All animals were injected with SAL and placed in the unpaired chamber of the apparatus for a 20-min session.

Day 5: Conditioned place preference test. Mice were allowed to freely explore the whole apparatus for a 10-min session, in a drug-free state. Time spent in each end-compartment, and total locomotor activity were obtained automatically.

2.5. Design and data analysis

Data were analyzed by a *split-plot* analysis of variance (ANOVA), where the litter was the block variable: prenatal treatment was a between-litters factor, whereas all other variables were within-litter factors. In order to study the acute AMPH effects, we analyzed activity data expressed within the drug-paired compartment on the first pairing day (see the procedure above). In order to study the incentive properties of AMPH, we analyzed data of the place-preference test. The dependent variable was the time spent in either the drug-paired or the SAL-paired side. The general design of the experiment was a three prenatal treatment (OIL, MXC, BPA) × 2 sex × 3 treatment (0, 1 and 2 mg/kg AMPH), as well as repeated measures on the same individual. A side variable (paired versus unpaired chamber) was used for place-preference data. Multiple comparisons were performed with Tuckey HSD test.

3. Results

No differences were found in body weight and sex ratio at birth as a consequence of prenatal treatment (data not shown).

3.1. Acute effects of AMPH (day 2 of the schedule)

Analysis yielded a main effect of sex ($F(1, 28) = 6.64$, $p < 0.05$), males showing higher overall levels of activity counts (data not shown). In both sexes, a main effect of treatment ($F(2, 42) = 14.6$, $p < 0.001$ for females and $F(2, 42) = 14.7$, $p < 0.001$ for males) confirmed the expected dose-dependent increment in locomotion induced by acute administration of the drug. No effects of prenatal exposure to chemicals were found, although a slight tendency towards an increased response to AMPH appeared in BPA and in MXC males, when compared to prenatal controls.

3.2. Conditioned place preference

ANOVA revealed a significant main effect of sex factor ($F(1, 20) = 8.57$, $p < 0.01$), thus allowing to carry out separate analyses for each sex. In males (Fig. 1 lower panel), a significant dose by side interaction was found ($F(2, 40) = 16.6$, $p < 0.001$). No significant or reliable effect of prenatal exposure to BPA or to MXC was found. Multiple comparisons confirmed that the expected CPP was produced by one dose of the drug in all prenatal-treatment groups. As for females (Fig. 1 upper panel), a significant dose by side ($F(2, 40) = 9.08$, $p < 0.001$), as well as a dose by side by prenatal exposure ($F(4, 40) = 2.51$, $p < 0.05$) interactions were found. This profile indicated that the AMPH-conditioned profile was a function of prenatal exposure. Specifically, at both drug doses OIL-exposed control females spent significantly more time in the paired than in the unpaired chamber. By contrast, the conditioned response to rewarding property of AMPH was completely dampened in BPA and MXC groups.

4. Discussion

As expected, acute AMPH injection on the first training day of the CPP paradigm induced a dose-related hyperactivity profile. Prenatal BPA or MXC exposure, however, was not associated with significant changes in the classical locomotor response to AMPH. With respect to AMPH-induced

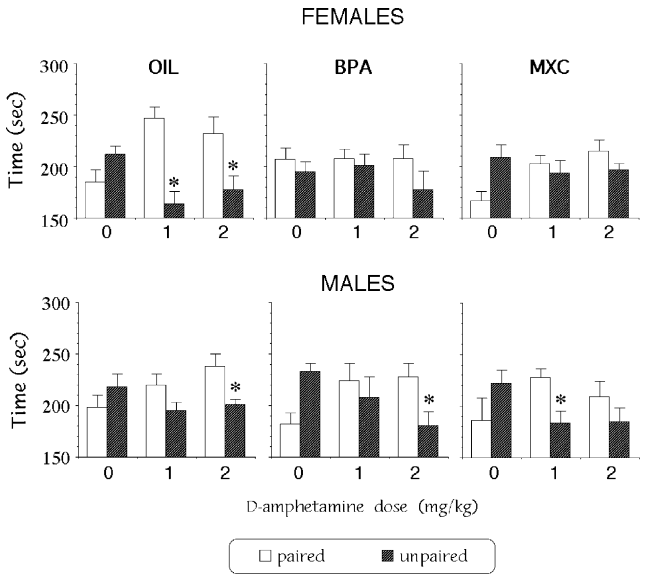

Fig. 1. Mean (±S.E.M.) time spent in drug-free state in the AMPH-paired or unpaired (i.e. SAL-paired) chambers of the apparatus by female (upper panel) and male (lower panel) mice exposed prenatally to BPA or MXC ($n = 10/12$). (*) Evidence of drug-induced place conditioning: $p < 0.05$ in multiple comparisons between time spent in either chamber.

place conditioning, females as a whole were more responsive than males, thus confirming previous results [38]. When compared to prenatal controls, BPA- as well as MXC-exposed females failed to show AMPH-induced conditioning. In other words, prenatal exposure to BPA or MXC was apparently responsible in female mice for a profound impairment of brain reward pathways targeted by the drug. Interestingly, no reliable or significant changes due to the prenatal treatment were evident for males. Recently, reduced novelty seeking and increased neophobia were found in female rats perinatally exposed to BPA (see [1]). Findings may well be seen as indexes of reduced reactivity or readiness to experience positive reinforcing effects of natural (environmental) or drug-mediated stimuli. The overall result of our studies is that prenatal exposure to the estrogenic pollutants BPA and MXC resulted in marked alterations in the psycho-pharmacological profile of female mice. It could be argued that BPA and MXC exposure impaired the subject adaptation to environmental challenges [11].

As for possible mechanisms, it should be noted that BPA exhibits weak estrogenic activity in adult rats of both sexes. Namely, BPA administration results in a significant increase in uterus and vagina weights in ovariectomized females [34], whereas it directly inhibits testicular functions and produces a reduction in the negative feedback of testosterone [59]. Long-term exposure of adult female rats to BPA induces modifications in α estrogen receptor immunoreactivity in various brain areas, which regulate reproductive and maternal behavior [3]. One study reported that intrauterine exposure to estradiol has a significant effect on the organization of monoamine systems within the foetal hypothalamus [32]. In previous studies, motor activity and motivation to explore were depressed at adulthood following maternal exposure to BPA [1,24]. This behavioral profile could be related to gender-specific alterations in the function of brain neurochemical systems involved in the response to AMPH. On this basis, it may be supposed that prenatal exposure to BPA interacted with some steps in the development and organization of the dopaminergic system during the prenatal period of female offspring.

The dopamine (DA) system has been reported to be affected by in utero and/or lactational exposure to endocrine disrupters (e.g. [55]). It is widely recognized that the mesolimbic and the nigrostriatal dopaminergic systems represent major structures of the CNS underlying hyperactivity, novelty-induced behavior, reward-based learning, and attention deficits [4,13,16]. A convincing body of evidence indicates that estrogen can modulate basal and amphetamine-stimulated levels of DA release in rodent striatum as measured by in vivo microdialysis [10]. In general, estrogen levels are positively correlated with striatal DA release. For example, basal and amphetamine-stimulated levels of DA are higher in female rats during behavioral estrus (i.e. physiological proestrus, when estradiol levels are high) relative to diestrus or to levels in ovariectomized rats [10]. Similar results are found when striatal DA content is measured, in that peak levels occur during behavioral estrus [21,46]. Although less thoroughly studied, circulating levels of gonadal hormones appear to have few behavioral effects in male rats. For example, adult castration has no effect on basal DA release [66], although these levels are still higher than those of ovariectomized rats [17]. Finally, unlike females, estradiol or testosterone treatment in gonadectomized males does not substantially alter amphetamine- or potassium-stimulated DA release [9,17,22,43].

Sexual differences in striatal tyrosine hydroxylase immunoreactivity have been described as early as embryonic day 16 in the rat [49]. Gonadal hormones may also play an essential role in organizing the underlying differences [36]. Sex differences in striatal DA content or density of D_1 and D_2 receptors during development [4,25] also imply that steroid hormones may play a role. Few studies, however have experimentally manipulated the developmental hormonal milieu and examined later striatal DA release. The results of one study imply that levels of androgens during the neonatal period are not important for establishing the sexual dimorphism in amphetamine-stimulated striatal DA release at adulthood [9]. For example, neonatal castration did not diminish in vitro DA release in adult males nor did neonatal ovariectomy and acute testosterone treatment alter DA release in adult females. Similar studies based on developmental estrogen treatment have been reported. For instance, developmental exposure to BPA has been shown to alter D_1 receptor expression and density in male mice [58].

In conclusion, exposure to BPA during ontogenetic critical periods interacts with some steps in the organization of the monoaminergic neural systems in the offspring. On the basis of the scientific literature, behavioral alterations reported in the present study could be ascribed to an altered

development of central monoaminergic pathways, but further work is needed to clarify the neural basis of long-term neurobehavioral alterations. As a general conclusion, the present findings provide evidence of long-term consequences of prenatal exposure to BPA and MXC at the level of neurobehavioral development. This should be a cause of concern for public health, confirming that exposure to low doses of environmental estrogens with a weak activity, during the period of sexual differentiation of the brain, can influence subsequent adult behavior. Our results indicate that further research is needed to better understand which levels of exposure would not be potentially dangerous for human health.

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