Bisphenol-A Administration during Pregnancy Results in Fetal Exposure in Mice and Monkeys

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MATERIALS AND METHODS

Mice of ICR/Jcl strain kept under 12 hr light/12 hr dark at 23–25°C were given a commercial diet (CE-2, CLEA, Tokyo, Japan) and tap water ad libitum. Japanese monkeys (Macaca fuscata) kept in a room with a temperature range between 10 to 25°C and a lighting schedule of 12 hr light/12 hr dark (light on at 6:00). All monkeys were fed every day with 160–180 g commercial monkey-chow (Oriental Yeast Co. Ltd., Tokyo, Japan) supplemented with sweet potatoes (ca. 100 g) three times a week. Water was given ad libitum. All procedures were

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INTRODUCTION

Bisphenol A (BPA) is a compound used for manufacture of the plastic polycarbonate. Estrogenic activity of BPA has been reported for over 50 years.1) Krishnan et al.2) reported BPA is released from autoclaved polycarbonate flasks and estrogenic activity of BPA is mediated via the estrogen receptor (ER). In serum from adult men, BPA showed a higher relative binding affinity than in a serum-free medium,3) showing that the estrogenic activity of BPA is more active in vivo than in vitro. Steinmetz et al.4) indicated that BPA induced the molecular and morphological alterations in uterus and vagina of adult rats. Results of some studies have shown that estrogenic chemicals including BPA and a synthetic estrogen, diethylstilbestrol (DES) can act at very low doses in the range of human and wildlife environmental exposures.5,6) Howiedeshall et al.7) demonstrated that a very low dose of BPA during pregnancy induces early onset of first estrus. ER binding affinity for BPA has been reported to have 1/10000 potency of 17β-estradiol (E2).8)

Perinatal exposure to natural and synthetic estrogens induces irreversible changes in estrogen target tissues.9,10) We recently found that low dose of BPA in utero accelerated vaginal opening in mice,11) and a large dose of BPA given neonatally induced ovary-independent vaginal epithelial changes.12) On the other hand, BPA was found in canned drinks in Japan,13) therefore, food contamination of BPA is possible. Developing fetus is more sensitive to estrogenic chemicals than adults in induction of various abnormalities.9,10) In this study, therefore, we investigated whether or not BPA cross the placenta and reach fetal tissues using mice and Japanese monkeys.

Placental transfer of bisphenol-A (BPA) was studied in mice and Japanese monkeys (Macaca fuscata). BPA was found in maternal and fetal sera, liver, brain, uteri, testes and placenta as early as 30 min after a single subcutaneous (s.c.) injection to 17 days of pregnancy in mice. BPA was also found in fetal liver, kidney, and brain of Japanese monkeys 1 hr after a single s.c. injection to 150 days of pregnancy. These results clearly indicate that the maternal placental barrier can not protect the fetus from the consequences of BPA exposure in these species.

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RESULTS AND DISCUSSION

In utero exposure to BPA (10 mg/kg BW) reduced ovulatory activity in mice at 40 days of age. BPA (10 and 100 mg/kg BW) exposed females gave birth when mated with untreated males, and the number of pups and sex ratio were not different from those of controls. Howdeshell et al. demonstrated that exposure to BPA (2.4 µg/kg BW) in utero advances puberty and increases body weight in female offspring. Gupta also showed that mice fed with BPA (50 mg/kg/day) and arochlor 1016 (50 µg/kg/day) had enhanced anogenital distance, increased prostate size, decreased epididymal weight and increased androgen receptor binding activity of the prostate. We recently found that BPA (20 µg/kg BW) from days 11–17 of pregnancy accelerated vaginal opening but not body weight gain in mice. Neontal exposure to a high dose of BPA (150 µg per pup) but not 15 µg BPA, induced ovary-independent vaginal changes, uterine epithelial strariification and polovular follicles, and infertility lacking corpora lutea. Several reports indicated that in utero exposure to BPA results in various effects on male and female mice as above and these results suggest that placental transfer of BPA into fetus. In fact, oral administration of BPA transferred from the maternal rat to the fetus. In mice, BPA was found in maternal and fetal sera, liver, brain, placenta, and fetal uteri and testes as early as 30 min after injection (Fig. 1). BPA concentrations in serum and liver of fetuses were higher than those of mothers. High BPA concentration in the fetal uterus may be correlated to the presence of ER in fetal uterus. BPA can be found in canned drinks up to 213 ppb and in river water in Japan as described. BPA and other chemicals, such as dioxins, PCBs, DDTs, BHC, cadmium, lead, and nonylphenol were found in the human umbilical cord. Thus, BPA levels were also investigated in primates, Japanese monkey. Japanese monkeys were injected with 50 mg BPA/kg BW on day 150 of pregnancy, and fetuses were collected 1 hr later. BPA was found in all organs investigated including fetal liver, kidney, brain and umbilical cord in BPA-treated monkey and even non-treated controls (0.02–22.8 µg/g) (Table 1). These values increased to 1.7–72.5 µg/g in BPA-injected monkeys 1 hr after the injection. These results indicate that the placental barrier can not protect the fetus from the consequences of direct BPA exposure. Organ specific accumulation is probable. BPA was found in commercial diet for monkeys (0.04–0.21 µg/g) and
even potatoes (0.01 µg/g). The concentration of BPA in food may contribute the BPA found in non-treated monkey fetal organs. In non-treated rat, BPA was detected in sera of both mother and fetus, and in breast milk and liver.\(^{21}\) Cytochrome P450s work to decrease estrogens,\(^{22,23}\) and glucuronosyltransferase (GT) catalyzes the glucuronide formation of BPA.\(^{24}\) Since the fetus does not express GT and BPA passes through the placenta, the fetus is indefensible against any effects by this exogenous estrogen. While the newborn rat poorly expresses GT, it is also possible that perinatal exposure to BPA could affect reproductive organ development. In conclusion, BPA can be found even in the commercial diet and BPA easily pass through the placenta and reaches into fetal organs. Thus, further studies are needed to determine BPA contamination sites in experimental animals and humans in order to devoid of BPA exposure.

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**REFERENCES**


