Transfer of bisphenol A across the human placenta

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OBJECTIVE: The objective of the investigation was to study placental transfer and conjugation of bisphenol A (BPA) across the human placenta.

STUDY DESIGN: Human placentae obtained from healthy term singleton pregnancies were utilized in a dual recirculating model of ex vivo placental perfusion. Seven placentae were perfused with BPA (10 ng/mL) added to the maternal perfusate for 180 minutes. Antipyrine and fluorescein isothiocyanate dextran were used as positive and negative controls, respectively, to validate integrity of the circuits. Concentrations of BPA and its conjugates were determined by liquid chromatography-mass spectrometry.

RESULTS: The transfer percentage for antipyrine and BPA were 25.5 ± 1.13% and 27.0 ± 1.88%, respectively, and the transfer index for BPA was 1.1 ± 0.09 after 180 minutes of perfusion. Only 3.2 ± 1.6% of BPA in the fetal compartment was in the conjugated form.

CONCLUSION: Bisphenol A at low environmentally relevant levels can transfer across the human placenta, mainly in active unconjugated form.

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Background and Objective

Bisphenol A (BPA) is a well-studied xenoestrogen with weak affinity for the estrogen receptor that is used in the preparation of polycarbonate plastics, dental sealants, and resins for can linings. Residual traces remain after manufacture and are slowly released, such that BPA in foodstuffs and drinking water is now the most significant source of exposure to synthetic xenoestrogens in New Zealand. Recent influential publications associating BPA exposure with several diseases have led to a ban of polycarbonate plastics in the production of baby bottles in Canada and to a switch by some manufacturers to BPA-free plastics.

The estrogenic action of BPA has been demonstrated in both in vivo and in vitro studies. BPA binds to both nuclear and membrane estrogen receptors and imparts both genomic and nongenomic steroid actions. Experiments in rodents have demonstrated that BPA can readily cross the placenta and can cause developmental abnormalities in the offspring. The transgenerational effects of BPA on the expression patterns of some testicular steroidogenic coregulators have been reported in the rat.

These and several other studies have shown the endocrine-disrupting activity of BPA, especially if there is fetal and/or neonatal exposure at vulnerable periods of development. BPA has been detected in maternal and fetal plasma, placenta, amniotic fluid, and follicular fluid. Studies have shown that hepatic 5' diphosphate glucuronyltransferases (UGT) can conjugate BPA into its glucuronide form, which is devoid of estrogenic action.

We hypothesized that BPA at environmentally relevant concentration can transfer across the human placenta in an active unconjugated form. The aim of this study was to determine placental transfer and conjugation of BPA at environmentally relevant concentrations.

Materials and Methods

A modified and fully validated dually perfused ex vivo placental perfusion system was used to study the transfer of BPA across the human placenta. The BPA concentration selected is within the range from the serum levels reported in pregnant women. The perfusion was continued for 3 hours and the samples from maternal and fetal reservoirs were collected at 30 minute intervals and stored at −80°C. A liquid chromatography–tandem mass spectrometry (LC-MS/MS) method was optimized in our laboratory to measure the bisphenol A content in the perfusates.

Results

The placentae studied maintained viability as well as metabolic activity throughout the perfusion period, as evident from constant glucose consumption, lactate production, and β-human chorionic gonadotropin (hCG) secretion. The values for glucose consumption and lactate production were 0.32 ± 0.06 μM/g per minute and 0.52 ± 0.1 μM/g per minute, respectively, in the maternal compartment and 0.32 ± 0.06 μM/g per minute and 0.35 ± 0.06 μM/g per minute, respectively, in the fetal compartment. We observed β-hCG secretion only in the maternal compartment (3.0 ± 0.9 mIU/g per minute); values in the fetal compartment were below detection level.

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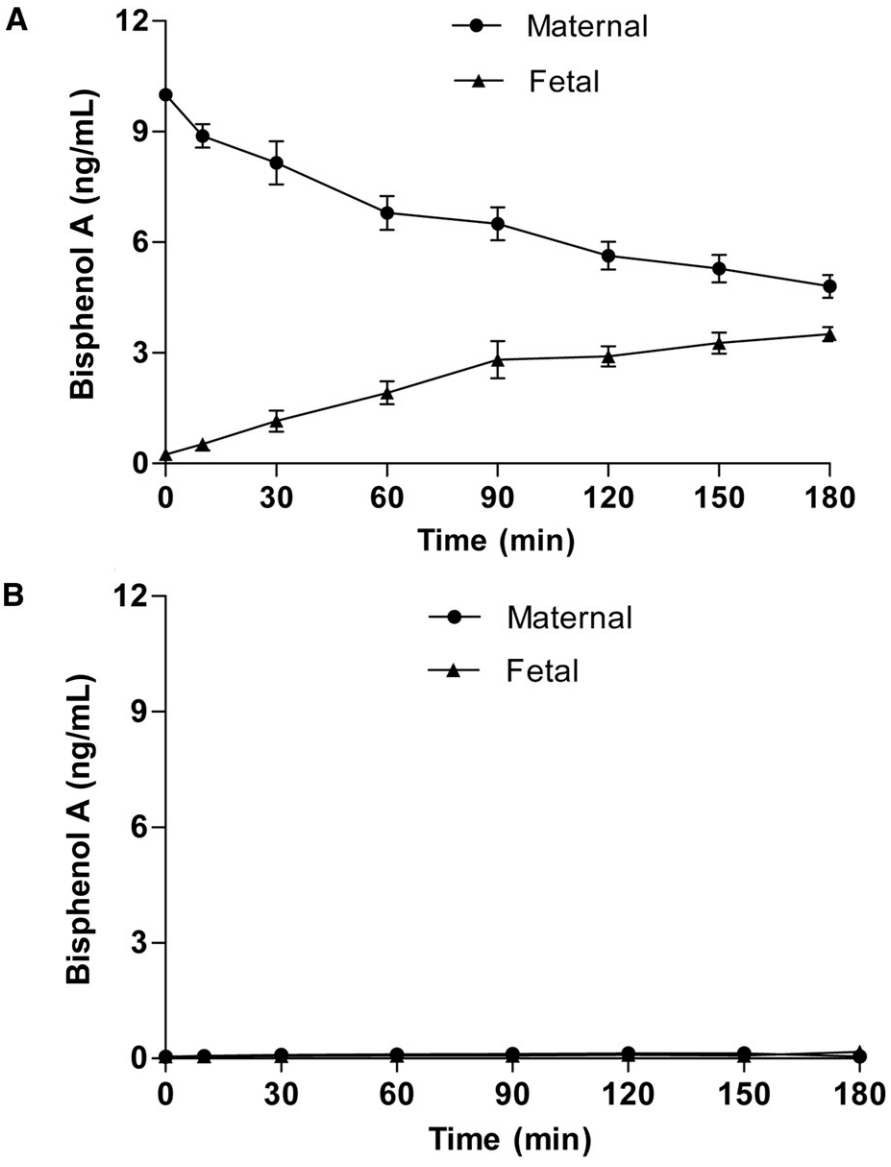
FIGURE
Transplacental transfer of BPA



BPA concentration in maternal and fetal compartment during 3 hours of perfusion as detected with LC-MS/MS **A,** BPA transfer (n = 7) **B,** and control placenta (n = 2). Data are presented as mean ± SEM.
BPA, bisphenol A; *LC-MS/MS*, liquid chromatography-tandem mass spectrometry.
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A gradual decline was observed in the concentration of BPA in the maternal compartment and a concomitant increase in the concentration of BPA in the fetal compartment. About 27% of BPA was detected in the fetal compartment within 180 minutes of perfusion. This clearly shows that BPA at low concentrations can cross the human placenta (Figure, A). No evidence of BPA release from the placental tissues was observed when the perfusates from control placenta were analyzed (Figure, B).

Comment

The present study has demonstrated for the first time that BPA at environmentally relevant concentrations can be transferred across the human placenta in an ex vivo human placental perfusion model. The major fraction of the compound transferred was in unconjugated form.

Substances are transferred across the placenta either by simple diffusion or through active transporters. Transport of materials across the placenta is also dependent on the molecular weight of the compound, protein binding, and lipophilicity. Our results indicate a rapid maternofetal transfer of BPA across the human placenta.

Our results thus imply that BPA is freely diffused across the human placenta at a rate that is significantly similar to that of antipyrine. BPA has been shown to be a substrate for the ABC-transporter P-glycoprotein (P-gp) in the intestine. In vitro BPA was also found to stimulate the drug efflux mechanism in a human placental cell line (BeWo, a choriocarcinoma cell line), indicating the possibility of regulation through P-gp. But the role of P-gp in the efflux of BPA has not yet been studied in the placenta. However, it has also been shown that placental expression of P-gp gradually decreases with gestational age with lowest expression at term. Hence, the apparent passive diffusion of BPA from maternal to fetal compartment in term placentae may be due to the fact that the expression of any drug efflux pumps is lowest at this time. Studies in pregnant rodents have also shown that BPA reached the fetal compartment within an hour of oral or intravenous administration, mostly in unconjugated form.

BPA after oral absorption has been shown to be conjugated to either glucuronide or sulfate form by hepatic enzymes in the liver. Conjugation of BPA has been shown to ablate the estrogenicity of BPA in vitro. Human term placenta expresses both uridine UGT and sulfotransferases required for the glucuronidation and sulfation of BPA. However, our data conclusively imply that only negligible amounts of BPA are being conjugated by the placenta. The results further suggest that fetus is exposed to free BPA.

Our data clearly show that BPA at maternal serum concentrations can transfer across the human placenta and imply that placental glucuronyltransferase or

sulfotransferase enzymes do not convert BPA into its conjugated form. The underdeveloped fetal liver cannot protect the fetus against this constant exposure. Hence, the fetus is potentially very vulnerable to the adverse effects of BPA, and it is critical to evaluate the harmful effects on health and well-being of the fetus from such an exposure.

CLINICAL IMPLICATIONS

- Bisphenol A (BPA) at environmentally relevant concentrations can be transferred across the human placenta.
- Hence, the fetus could be constantly exposed to BPA at vulnerable windows of human development. ■