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# Biotransformation of Bisphenol A and Its Adverse Effects on the Next Generation

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Jumpei Fujiki and Hiroshi Yokota

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.78275>

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## Abstract

Although we are exposed to many chemical substances in routine daily life, the body has metabolic systems capable of detoxifying and eliminating these chemicals. Bisphenol A (BPA) is an endocrine disrupter of great concern because of its estrogenic activity, but studies have indicated no severe adverse effects in adult rodents exposed to BPA due to metabolic detoxification. BPA is metabolized by glucuronidation mediated by phase II enzymes such as UDP-glucuronosyltransferase. Numerous recent studies in rodents have indicated that maternal BPA exposure causes adverse effects in offspring. It was also shown that bisphenol analogs are efficiently absorbed via the oral route and distributed to the reproductive tract in pregnant rats, with its residue capable of crossing the placental barrier in the late stage of gestation. Both animal and human studies have demonstrated that BPA and the BPA metabolite BPA-GA are detectable in fetal and amniotic fluid, suggesting the presence of a placental transfer mechanism. In this review, we discuss the pharmacokinetics of BPA, particularly its (1) metabolism and disposition in the intestine, (2) metabolism and disposition in the liver, and (3) transfer from maternal tissues to the fetus.

**Keywords:** bisphenol A, UDP-glucuronosyltransferase (UGT), multidrug resistance-associated protein (MRP), organic anion-transporting polypeptide (Oatp), xenobiotic-metabolizing enzymes (XMEs), liver perfusion,  $\beta$ -glucuronidase

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## 1. Introduction

Bisphenol A (BPA; 2,2-bis[4-hydroxyphenyl]propane) is an industrial chemical widely used in the manufacture of polycarbonate plastics and epoxy resin liners for aluminum cans [1–7]. BPA is an endocrine-disrupting chemical (EDC) that has been demonstrated to affect

reproductive organ development [7–9], brain development [10–15], metabolic diseases [16], and postnatal behavior [17–19]. These adverse effects are thought to be due to disturbed signaling mechanisms involving estrogen, androgen, and thyroid hormone.

BPA introduced into the body orally must pass through the gastrointestinal tract and liver before arriving at target tissues such as the uterus, testes, or fetus. To elucidate the mechanism responsible for the adverse effects of BPA, it is essential to clarify the fate of the compound during its passage through the hepatointestinal pathway. The hepatointestinal pathway serves as a protective barrier against a variety of potentially harmful chemicals due to the activity of potent xenobiotic-metabolizing enzymes (XMEs), which can be classified into three main categories [20]. The first category consists of phase I enzymes, mainly of the cytochrome P450 (CYP) family [21]. Most drugs are metabolized by CYPs, either during detoxification or due to the activation of a pathway for an inactive prodrug. The second XME category consists of what are referred to as phase II enzymes [22–24]. These enzymes usually conjugate phase I products but can also conjugate other intermediate compounds and intracellular substrates, such as steroids and bilirubin. The third category of XMEs consists of drug transporters, which are membrane-bound proteins involved in drug uptake or excretion [25, 26].

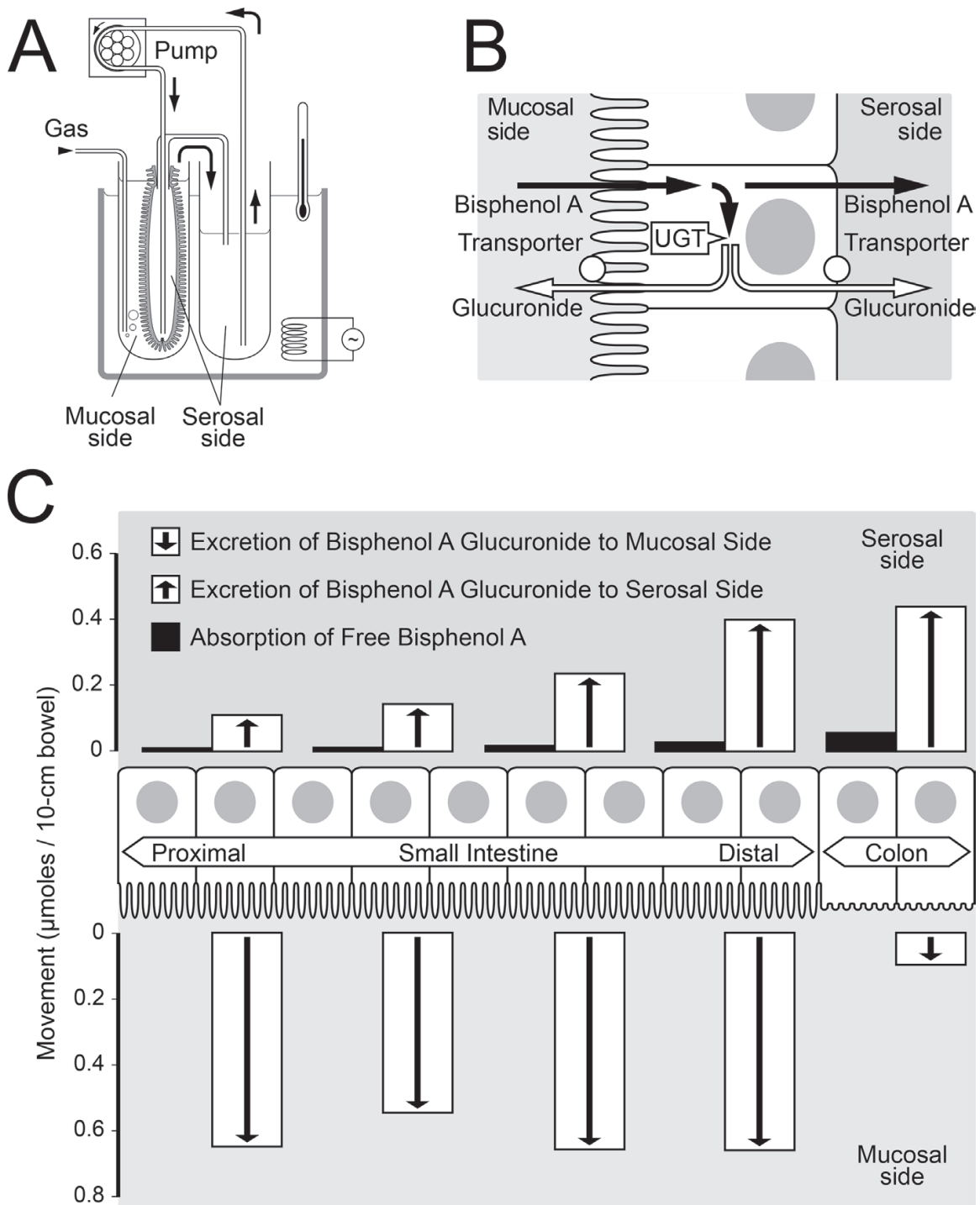
Detoxification enzymes have been shown to play a pivotal role in the elimination of ingested chemicals from the intestinal wall and liver. In rat liver, BPA is metabolized by phase II enzymes via glucuronidation, which is mediated by UDP-glucuronosyltransferase (UGT, Enzyme Classification 2.4.1.17), primarily the UGT2B1 isoform [27]. Glucuronidation is a major elimination process that converts lipophilic substrates to hydrophilic molecules that are readily excreted via the bile and urine [20, 28]. Glucuronidation is the main pathway by which BPA is metabolized to a hydrophilic form lacking estrogenic activity. We were the first to report that BPA is highly glucuronidated in rat liver [27]. To clearly elucidate the metabolism and disposition of BPA in the body, we thought it was important to conduct an investigation at the tissue level, and we therefore carried out tissue perfusion experiments.

In this chapter, we discuss the metabolism and disposition of BPA, particularly in the gastrointestinal tract and liver, as well as why the fetus is so easily affected by BPA. The investigation specifically focused on the following: (1) metabolism and disposition of BPA in the intestine, (2) metabolism and disposition of BPA in the liver, and (3) transfer of BPA from maternal tissues to the fetus.

### **1.1. Metabolism and disposition of BPA in the intestine**

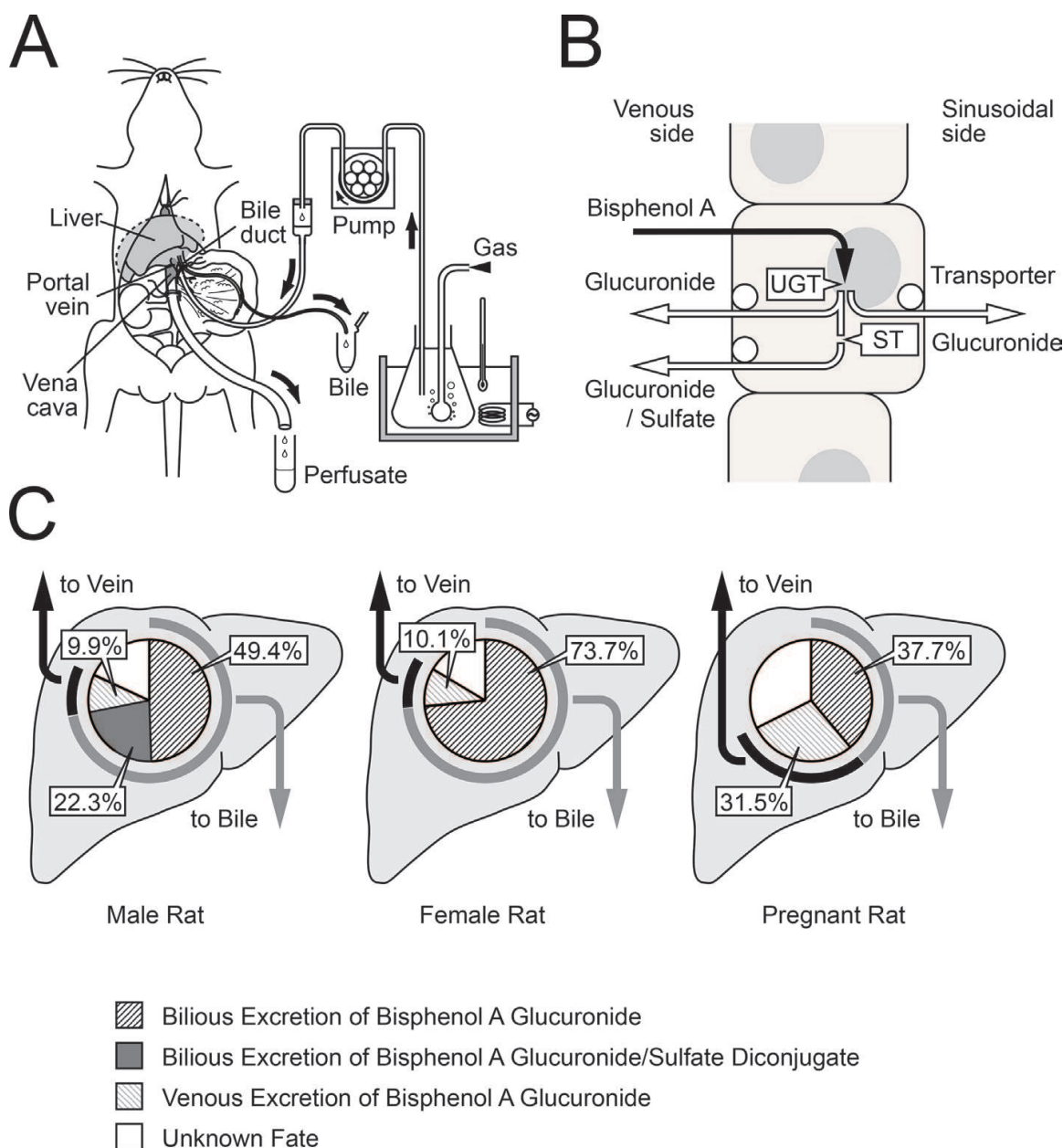
This section focuses on the absorption and metabolism of BPA in the intestine. For a thorough investigation of the metabolism of BPA in the intestine, we adopted a method using a segment of everted intestine (**Figure 1A**) [29]. We find that in the intestine of Sprague-Dawley rats exposed to BPA, (1) most of the compounds absorbed by the intestine are glucuronidated within the intestinal wall and (2) the resulting GA is preferentially eliminated into the mucosal side of the small intestine and the serosal side of the colon (**Figure 1B and C**).

These results suggest that the proximal intestine plays a highly protective role against ingested BPA. BPA was highly glucuronidated during its passage through the lumen of the rat intestine, with most of the compounds being excreted to the mucosal side as BPA-GA, which



**Figure 1.** Overview of the metabolism and disposition of BPA in the intestine. (A) Schema of method using a segment of everted intestine. (B) Metabolism and disposition of BPA in small intestinal mucosal cells. BPA was highly glucuronidated through the lumen of the rat intestine. (C) Summary of BPA metabolism in the intestinal tract. Mucosal excretion of BPA-GA greatly exceeded serosal excretion in the proximal intestine; however, the direction of elimination was reversed in the colon.

is low in estrogenic activity (**Figure 2B**) [30]. This was particularly evident in the proximal jejunum, where mucosal excretion of BPA-GA greatly exceeded serosal excretion. Therefore, it appears that the proximal jejunum defends against the potentially adverse effects of orally



**Figure 2.** Overview of the metabolism and disposition of BPA in the liver. (A) Schema of the liver perfusion method. (B) Metabolism and disposition of BPA in hepatocytes. (C) Summary of BPA metabolism in the liver. BPA is conjugated primarily to monoglucuronide and partially BPA-glucuronide/sulfate diconjugate in males, but otherwise almost no diconjugate was detected in female rats. Most metabolites were excreted into the bile, but during pregnancy, biliary excretion of BPA-GA decreases, and reciprocally, venous excretion increases.

introduced BPA by limiting entry of the free compound into the bloodstream and curtailing exposure to the middle and distal parts of the intestine. These results are in line with previous reports of low exposure to the compound in association with the oral intake of BPA [31–36]. Comparing the concentration-time profiles of BPA in the blood of F344 rats exposed to the compound intraperitoneally with those of rats exposed orally, Pottenger et al. [31] found that oral administration results in lower exposure to unconjugated BPA. In light of these findings, the diminution of exposure to unconjugated BPA on oral administration may be ascribed to



the high degree of glucuronidation of the compound in the proximal intestine, which is the foremost barrier to damage from oral administration. We previously reported that BPA glucuronidation in the liver is mediated by UGT2B1, an isoform of UDP-glucuronosyltransferase, and that this isoform is not expressed in rat intestine [27]. Generally, the UGT2B family glucuronidates steroid hormones [37]. In humans, several UGT isoforms are known to conjugate BPA. UGT2B15 reportedly has the highest activity, with lower activities reported for recombinant UGT1A1, UGT1A3, UGT1A9, UGT2B4, and UGT2B7 [38]. The results of a recent analysis of a mouse cell line in which all UGT 2B genes were deleted suggest that members of the UGT1 family play a major role in BPA glucuronidation [39], which in turn suggests that the UGT1 family also plays a major role in intestinal BPA glucuronidation.

Although BPA-GA was excreted into the mucosal side of the small intestine, the direction of elimination was reversed in the colon, where excretion was into the serosal side (**Figure 2C**). ATP-dependent transporters have been described as mediating the transport of GA-conjugated compounds across the cell membrane [40]. In rat liver, a member of the ATP-binding cassette (ABC) transporter family, namely multidrug resistance-associated protein (MRP), is capable of mediating transmembrane excretion of a wide range of amphipathic compounds, including bilirubin-, estrogen-, and xenobiotic-GA [41]. In rat intestine, MRP2, localized in the apical domain of enterocytes, is distributed in the proximal intestine [42], and MRP3, localized in the basolateral domain, is distributed mainly in the ileum and colon [43]. Intriguingly, the apical and basolateral directions of BPA-GA excretion in the present study paralleled the distribution patterns of MRP2 and MRP3, respectively. Other reports have indicated that MRP2 is highly expressed in the proximal intestine, whereas MRP3 and MRP4 are highly expressed in the colon [44]. As MRP3 and MRP4 are expressed in the basolateral domain of the liver and intestine [45], the supposition may be made that the elimination direction of BPA-GA is governed by the distribution of an organic anion transporter system such as MRP.

As large amounts of BPA-GA are eliminated from the lumen, the excreted GA would presumably flow into the distal intestine with the luminal contents. In the colon, GA would most likely be deconjugated by lumen bacterial  $\beta$ -glucuronidase, an enzyme known to generate toxic and carcinogenic substances [46]. Deconjugation by lumen bacterial  $\beta$ -glucuronidase is known to be involved in the reactivation of an antitumor compound derived from irinotecan [47]. Furthermore, as excreted BPA-GA is deconjugated by bacterial  $\beta$ -glucuronidase in the cecum, free BPA is detected only in the colon and feces [48]. In light of these previous findings, the notable absorption and transport of unconjugated BPA to the serosal side of the rat colon observed in this study suggests that deconjugated BPA is eventually reabsorbed by the colon.

Generally, the paramount issue in studies of the adverse effects of BPA concerns oral exposure to the chemical in low doses [7, 49]. Although Rubin et al. [50] described adverse effects in rat offspring after maternal administration, other studies have found no adverse effects [51, 52]. Therefore, the toxicity of low doses of BPA remains controversial. We believe that an animal's sensitivity to ingested BPA reflects the conditions inside the intestine (e.g., the luminal contents and composition of the bacterial flora). Further studies are required to clarify the correlation between the catalytic reactivation of BPA-GA by the luminal flora and any resulting adverse effects.

## 1.2. Metabolism and disposition of BPA in the liver

Because environmental estrogens introduced orally are absorbed by the gastrointestinal tract and consequently the liver before being distributed throughout the body, it is important to trace their fate before they reach the reproductive organs. This section focuses on the metabolism and disposition of BPA in the liver. To facilitate thorough investigation of the metabolism of BPA in the liver, we adopted a liver perfusion assay in a previous study (**Figure 2A** and **B**) [53–55]. The results showed that (1) in Sprague-Dawley rats, most BPA absorbed by the intestine is likely glucuronidated in the liver, (2) the resulting BPA-GA is excreted into the bile and venous blood, and (3) in pregnant rats, there is a slight but significant decrease in bilious excretion of BPA-GA, which results in a reciprocal increase in venous excretion (**Figure 2C**).

These findings are in line with those from a study reporting that BPA added to the culture medium of isolated hepatocytes is highly metabolized to BPA-GA [56]. Moreover, previous studies of BPA pharmacokinetics and metabolism in rats provided evidence that the major metabolite in the plasma is BPA monoglucuronide conjugates [31–33]. Therefore, glucuronidation is a major pathway of BPA metabolism in the liver. After glucuronidation, the conjugates must be excreted from the hepatocytes into the bile and venous blood. Intriguingly, in male rats, approximately one-fourth of infused BPA was eliminated as a GA/sulfate diconjugate, whereas this diconjugate was virtually absent in female rats (**Figure 2**). Suiko et al. reported that BPA is conjugated with sulfate by several forms of human sulfotransferase [57]. We recently reported the results of rat liver perfusion experiments in which we found that BPA is conjugated primarily to monoglucuronide; in males, we found that diconjugate (GA/sulfate diconjugate) production occurs under conditions of high-dose BPA exposure [53]. These findings agree with those from a previous study in which BPA added to the medium of isolated hepatocytes was metabolized into both monoglucuronide and diconjugate; moreover, almost no diconjugate was detected in female rats [56]. BPA sulfoconjugation is mediated by phenol sulfotransferase isoforms of the SULT1 family [58]. One member of the SULT1 family, SULT1A1, exhibits a high conjugation activity toward BPA [59]. The expression level of SULT1 family enzymes is estimated to be higher in male than in female rats [60].

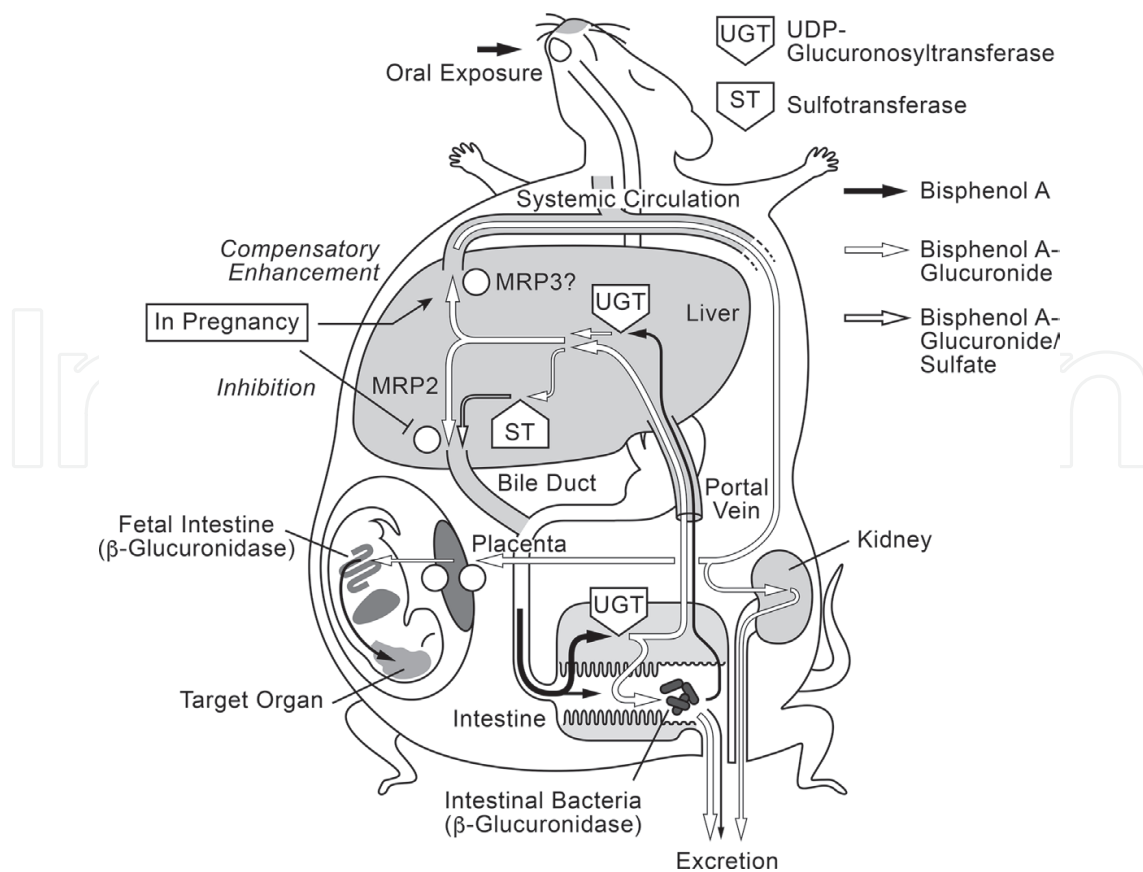
During pregnancy, the bilious excretion of BPA-GA decreases, and reciprocally, venous excretion increases. A wide variety of drug conjugates are transported by members of the ABC transporter family known as glutathione-S-conjugate export pumps. MRP2, a pump that is expressed primarily in the canalicular membrane of hepatocytes, transports drug GA to the bile [45]. Both the hepatic expression and function of MRP2 decrease in pregnant rats [61]. Regarding sinusoidal excretion, MRP1 and MRP3 have been shown to mediate chemical-GA transport [62–64], and the expression of MRP3 is attenuated in pregnancy [61]. Together with our previous results regarding liver perfusion in Eisai hyperbilirubinemic rats [54], these findings give rise to the view that a low expression of MRP2 in pregnancy limits the transport rate of BPA-GA into the bile and that sinusoidal transport systems such as MRP1 and MRP3 compensate by transporting GA to the venous blood.

## 1.3. Transfer of BPA from the maternal side to the fetus

Venous BPA-GA excreted from the liver enters the systemic blood circulation. Pottenger et al. [31] showed that BPA-GA can be detected in the urine after administration of

BPA; therefore, BPA-GA is excreted into the urine. However, certain organs, such as the lungs, small intestines, and placenta, show a high  $\beta$ -glucuronidase activity [65, 66]. BPA-GA can be cleaved in these organs, and it can be predicted that the resultant BPA moves to the lower organs supplied by the bloodstream. In the placenta,  $\beta$ -glucuronidase activity leads to fetal exposure to BPA. Kushari and Mukherjea [67] reported that placental  $\beta$ -glucuronidase activity is present during early gestation in humans, which is a highly vulnerable period for the developing fetus. An important concern, however, is that previous investigators reported that the placenta exhibits a minimal glucuronidation activity [68, 69]. We also demonstrated that BPA-GA is transported to the fetus following uterine perfusion and that BPA-GA and deconjugated BPA can be detected in the fetus and amniotic fluid due to a high deconjugation activity and vulnerable drug metabolism in the fetus [70]. After oral administration of 10 mg/kg 14C-BPA to GD16.0 rat mothers, Domoradzki et al. found that BPA-GA was concentrated in the fetus [32]. Kurebayashi et al. also detected radioactivity in GD18 fetal tissues 24 h after oral administration of 14C-BPA to pregnant rats, but they found no radioactivity in GD13 or GD15 fetuses [35]. Therefore, BPA-GA may be transferred across the placenta to the fetus by placental transporters that mediate the transfer of essential endogenous physiologic estrogenic compounds (**Figure 3**).

BPA is highly glucuronidated through the lumen of the rat intestine. In the intestine, serosal excretion of BPA metabolite is probably BPA-GA, and partially free BPA may be also transported into the portal vein. In the liver, BPA is conjugated primarily to monoglucuronide and



**Figure 3.** Illustration of the metabolism and disposition of BPA during pregnancy.



partially BPA-glucuronide/sulfate diconjugate in males. During pregnancy, bilious excretion of BPA-GA decreases, and reciprocally, venous excretion may increase through MRP. BPA-GA remaining in systemic blood circulation is metabolized by placental or fetal  $\beta$ -glucuronidase, and the resultant BPA would permeate the fetal tissues. MRP, multidrug resistance-associated protein; UGT, UDP-glucuronosyltransferase; ST, sulfotransferase.

Some members of the Oatp [71–73] and Mrp [74, 75] transporter families are known to transport conjugates of steroid hormones such as DHEAS and 17 $\beta$ -estradiol-GA, suggesting that BPA-GA is transported across the placenta by these transporters. In light of the studies cited above and our present results, we surmise that if BPA-GA remaining in systemic blood circulation is metabolized by placental or fetal  $\beta$ -glucuronidase, the resultant BPA would permeate the fetal tissues (**Figure 3**). Due to a low UGT2B1 expression in fetal rat liver, we also reported that this metabolic system is weak in the fetus [70, 76, 77]. Numerous recent studies in rodents have found that maternal BPA exposure causes adverse effects in the offspring [17, 78–84]. In light of these findings, the present results suggest that the risk of BPA exposure to the fetus is high, despite preservation of BPA glucuronidation in the maternal liver.

## 2. Conclusion(s)

Many reports have suggested that human health may be affected by exposure to even low levels of BPA, especially during the gestation period. However, the detailed mechanisms of BPA's effects remain unknown. To further elucidate the mechanism governing the detrimental effects of EDCs on target organs, it is essential to clarify both the metabolism and elimination pathways of such chemicals in the body. However, BPA is highly glucuronidated in the intestine and liver, and the resultant formation of BPA-GA prevents a complete understanding of metabolism and disposition by facilitating deconjugation during enterohepatic circulation and systematic circulation in the body. Given that exposure to BPA could adversely affect the fetus in pregnant animals, it is critical that further work be done to determine the fate of venous GA compounds in the complete BPA pathway before excretion.

In modern society, we are continually exposed to many chemical substances. We have to deal with all of these chemicals to ensure good health. Many studies of the effects of chemical substances have focused only on terminal mechanisms. We originally developed the prominent drug metabolism systems to eliminate various chemicals in the process of evolution. The various mechanisms that determine the effects of EDCs can only be productively discussed after a more complete understanding of their metabolism systems is achieved. At that point, new precautions to avoid the risks of adverse effects could be developed.

## Acknowledgements

This study was supported by the Rakuno Gakuen University Research Fund (No. 2018-04).

## Conflict of interest

The authors declare no conflict of interest.

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