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Inhibition of SLC drug transporter activities by environmental bisphenols

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The plastic component bisphenol A (BPA) is suspected to exert deleterious effects towards human health and targets various cellular and molecular pathways, including activity of ATP-binding cassette drug transporters. The present study was designed to determine whether BPA and some derivatives, like its substitutes bisphenol F (BPF) and bisphenol S (BPS) and the flame retardant tetrabromobisphenol A (TBBPA), may additionally interact with solute carrier (SLC) drug transporters. Activities of the various following SLC transporters were inhibited in a major way (by >60%) by 100 μM bisphenols: OCT1 and MATE1 (by BPA and TBBPA), OATP1B1 (by BPA, BPF and TBBPA), OATP1B3 and NTCP (by TBBPA) and OAT3 (by BPA, BPF, BPS and TBBPA); by contrast, activities of other transporters were not impacted (MATE2-K) or were stimulated (notably OCT1 by BPS and OCT2 by BPF). Transporter inhibitions due to bisphenols were concentrations-dependent, with half maximal inhibitory concentrations (IC_{50}) ranging from 0.5 μM to 73.5 μM. BPA was finally shown to be not transported by OAT3, although inhibiting this transporter in a competitive manner. Taken together, these data indicate that bisphenols interact with SLC transporters, at concentration levels however rather higher than those occurring in humans in response to environmental exposure.

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1. Introduction

Bisphenol A (BPA) is a synthetic chemical, largely used as a monomere in the production of polycarbonate plastics and epoxy resins, and by this way among the highest-volume chemicals produced worldwide. BPA is found in many consumer products, including food containers, paper products like thermal paper, water pipes and medical equipment (Halden, 2010). Humans are consequently widely exposed to this chemical, *via* dietary and non-dietary sources (Kang et al., 2006). Importantly, such an exposure is now thought to cause various deleterious effects for health (Rochester, 2013; Srivastava et al., 2015). BPA, through acting as a xeno-estrogen (Ben-Jonathan and Steinmetz, 1998), may thus exert reproductive and developmental toxicity (Golub et al., 2010; Peretz et al., 2014); it may also contribute to metabolic and cardiovascular diseases (Lang et al., 2008), may impair immunity (Jochmanova et al., 2015) and is suspected to have carcinogenic properties (Thompson et al., 2015). Such toxic effects have led to governmental restrictive regulations on the production and usage of BPA in North America and the European Union (Birnbaum et al., 2013). This also stimulates the development and production of alternative substances to replace BPA in a myriad of applications. Among such BPA substitutes, bisphenol analogues like bisphenol F (BPF) and bisphenol S (BPS) are major ones, even if they exhibited estrogenic and/or anti-androgenic activities similar to those of BPA (Chen et al., 2016). Endocrine-disrupting effects have additionally been reported for tetrabromobisphenol A (TBBPA), another bisphenol derivative, widely used as a brominated flame retardant in printed circuit boards and to which humans are also highly exposed (Birnbaum and Staskal, 2004).

Besides classical nuclear estrogen receptor alpha and beta, various molecular targets of BPA have been described, notably at the plasma membrane level. BPA thus interacts with ion channels and ATP-binding cassette (ABC) membrane transporters (Deutschmann et al., 2013; Soriano et al., 2016), suggesting that transport across plasma membrane may represent one of the cellular processes with which bisphenols interfere. In this context, it is noteworthy that main ABC drug efflux pumps have been shown to be targeted by bisphenols. Breast cancer resistance protein (BCRP/*ABCG2*) activity is thus inhibited by BPA and TBBPA (Dankers et al., 2013). TBBPA additionally inhibits P-glycoprotein

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(*ABCB1*), multidrug resistance-associated protein (MRP) 1 (*ABCC1*) and MRP4 (*ABCC4*) (Dankers et al., 2013). By contrast, BPA stimulates P-glycoprotein activity (Jin and Audus, 2005), without however affecting P-glycoprotein expression (Peyre et al., 2014), whereas levels of other drug detoxifying proteins like hepatic cytochromes P-450 may be impaired by BPA, but not by TBBPA (Germer et al., 2006; Vrzal et al., 2015). Importantly, BPA, but not TBBPA, is transported by BCRP (Dankers et al., 2013); BPA is also a potential substrate for MRP2 (*ABCC2*) and MRP3 (*ABCC3*) (Mazur et al., 2012). These drug efflux pumps may therefore participate in the elimination of BPA and conjugated BPA metabolites, notably at the liver level (Moscovitz et al., 2016).

In addition to interacting with membrane ABC drug transporters, bisphenols may interact with activity of solute carrier (SLC) drug transporters. The fact that BPA has been recently shown to inhibit activity of organic anion transporting polypeptide (OATP/*SLCO*) 1d1 (*Slco1d1*) in zebrafish fully supports this hypothesis (Popovic et al., 2014). Such potential interactions of bisphenols with SLC transporters remain however very poorly characterized, although SLC drug transporters represents key-actors of xenobiotic elimination pathway, notably in the liver and kidney (Giacomini et al., 2010; Lecureur et al., 2000). Most of SLC drug transporters primarily mediate drug uptake and, by this way and in concert with ABC transporters, they control intracellular levels of drugs, notably in hepatocytes (Planchamp et al., 2007). Their inhibition may be the source of numerous drug-drug interactions (DDI) (Koepsell, 2015; Shitara et al., 2005). The present study was therefore designed to analyze the possible interactions of various environmentally relevant bisphenols, *i.e.*, BPA, BPF, BPS and TBBPA, with activities of main human SLC drug transporters notably expressed in the liver, *i.e.*, organic cation transporter (OCT) 1 (*SLC22A1*), OATP1B1 (*SLCO1B1*), OATP1B3 (*SLCO1B3*), sodium/taurocholate co-transporting polypeptide (NTCP/*SLC10A1*) and multidrug and toxin extrusion protein (MATE) 1 (*SLC47A1*), or in the kidney, *i.e.*, OCT2 (*SLC22A2*), organic anion transporter (OAT) 1 (*SLC22A6*), OAT3 (*SLC22A7*) and MATE2-K (*SLC47A2*). Our data indicate that most of these SLC transporters constitute targets for bisphenols, especially for BPA and TBBPA.

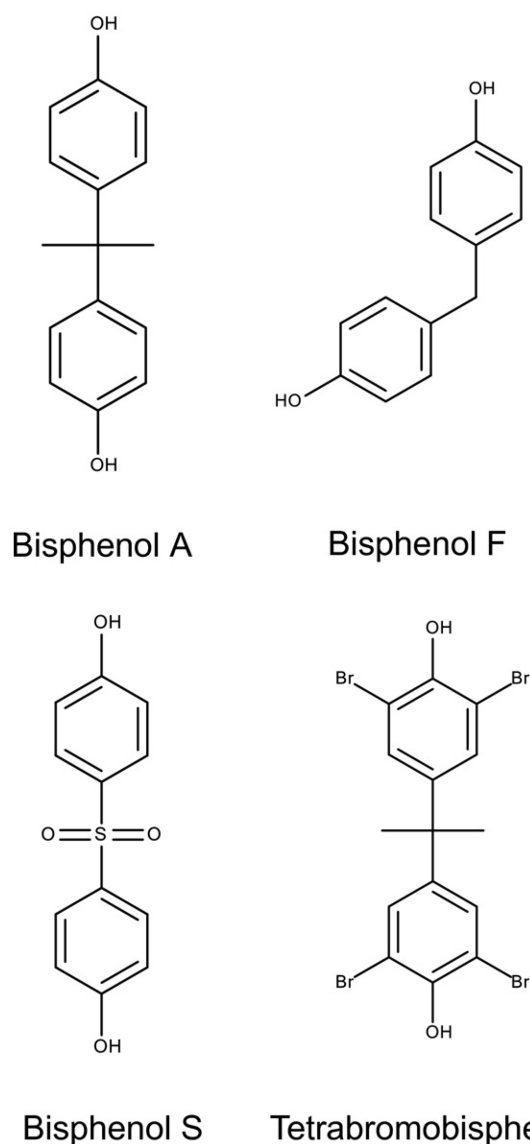

Fig. 1. Chemical structures of bisphenols.

2. Materials and methods

2.1. Chemicals and reagents

BPA, BPF, BPS and TBBPA were provided by Sigma-Aldrich (Saint-Quentin Fallavier, France), as well as verapamil, probenecid, fluorescein, bromosulfophthalein (BSP) and amitriptyline. Chemical structures of bisphenols are shown in Fig. 1. Some of their basic molecular properties, including molecular weight, LogP predicted using the XLogP3 method (Cheng et al., 2007), counts of hydrogen bond donors, hydrogen bond acceptors and rotatable bonds, and topological polar surface area, were given by PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and are indicated in Supplementary Table 1. [1-^{14}C]-tetra-ethylammonium bromide (TEA) (sp. act. 3.5 mCi/mmol), [6, 7-^{3}H(N)] estrone-3-sulfate (E3S) (sp. act. 57.3 Ci/mmol), [^{3}H(G)]-taurocholic acid (TC) (sp. act. 5.0 Ci/mmol), *p*-[glycyl-1-^{14}C]-aminohippuric acid (PAH) (sp. act. 50.4 Ci/mmol) and [bis 2,6-^{3}H]-BPA (sp. act. 51.0 Ci/mmol) were from Perkin-Elmer (Boston, MA, USA). All other chemicals and reagents were commercial products of the highest purity available.

2.2. Cell culture

HEK293 cells overexpressing OCT1 (HEK-OCT1 cells), OCT2 (HEK-OCT2 cells), MATE1 (HEK-MATE1 cells), MATE2-K (HEK-MATE2-K cells) or NTCP (HEK-NTCP cells) and control HEK293 cells (HEK-MOCK cells), whose generation and functional characterization have already been described (Jouan et al., 2014; Le Vee et al., 2015; Mayati et al., 2015; Sayyed et al., 2016), were routinely cultured in DMEM medium supplemented with 10% fetal calf serum (v/v), 20 IU/mL penicillin, 20 μg/mL streptomycin, 1% (vol/vol) MEM non-essential amino acids solution (Life Technologies) and 1 μg/mL insulin. HEK293 cells overexpressing OAT1 (NM_004790) (HEK-OAT1 cells) or OAT3 (NM_004254) (HEK-OAT3 cells) were prepared by transduction of HEK293 cells by a lentiviral pLV-EF1-hOAT1-hPGK-GFP or pLV-EF1-hOAT3-hPGK-GFP vector, as previously reported (Jouan et al., 2014). Construction of the lentiviral vectors, production of lentivirus supernatants, transduction of HEK293 cells, cloning and initial characterization of HEK-OAT1 and HEK-OAT3 cells were performed by Vectalys (Labège, France). HEK-OAT1 and HEK-OAT3 cells were routinely cultured in DMEM medium as described above.

OATP1B1- and OATP1B3-transfected CHO cells as well as parental wild-type CHO cells were cultured in DMEM-low glucose containing 20 IU/mL penicillin, 20 μg/mL streptomycin, 10% (vol/vol) fetal calf serum and 50 μg/mL proline, as already reported (de Graaf et al., 2011). G418 (500 μg/mL) was specifically added in culture media for OATP1B1- and OATP1B3-transfected CHO cells, whose functional transport features have been previously characterized (Gui et al., 2008; Treiber et al., 2007).

Human differentiated hepatoma HepaRG cells, which exhibit functional expression of OATPs (Le Vee et al., 2006), were routinely cultured in Williams' E medium (Life Technologies) supplemented with 10% (vol/vol) fetal calf serum, 20 IU/mL penicillin, 20 μg/mL streptomycin,

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