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Role of polybrominated diphenyl ethers in thyroid hormone transport disruption

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Polybrominated diphenyl ethers (PBDEs) are extensively used brominated flame retardants and are considered endocrine-disrupting chemicals (EDCs) due to their structural similarity with thyroid hormones. The growing concerns regarding the potential endocrine-disrupting effects of polybrominated diphenyl ethers (PBDEs) on human health have prompted a need for detailed investigations into their molecular interactions with critical proteins involved in hormone transport and regulation. Thyroxine-binding globulin (TBG) plays a pivotal role in the transport and regulation of thyroid hormones, which are essential for numerous physiological processes, including metabolism, growth, and development. The aim of this study was to investigate the structural interactions of commonly detected four PBDEs ligands, BDE-28, BDE-85, BDE-154 and BDE-183 against thyroxine-binding globulin (TBG). The indicated four PBDEs ligands were subjected to structural binding characterization against the TBG ligand binding pocket using Schrodinger's induced fit docking. Further, the structural analysis of TBG-ligand complexes including the molecular interaction and binding energy estimation was also performed. The results indicated the stable and tight binding of all four PDBE ligands in TBG ligand binding pocket and high percentage of commonality in interacting amino acid residues with that of TBG native ligand, thyroxine (T4). Furthermore, the estimated binding energy values for BDE-154 and BDE-183 were very close to each other and approximately same as that of T4. However, the predicted values for the remaining two ligands, BDE-28 and BDE-85 were lower compared to the estimated values of T4. In conclusion, on a preliminary basis, the results of our study suggested that the indicated PBDEs, especially BDE-154 and BDE-183, have the potential to interfere in the binding of thyroid hormones to TBG. This interference disrupts the circulatory transport of thyroid hormones which might have implications in thyroid associated health outcomes.

Keywords: Flame retardants, Polybrominated diphenyl ethers, Structural studies, Thyroid hormone transport, Endocrine disruption

Flame retardants constitute a diverse range of synthetic chemical compounds added to combustible products to either prevent the start or slow down the propagation of fire[1]. Polybrominated diphenylethers (PBDEs), a major class of brominated flame retardants, have been the most common choice due to their cost-effective nature and higher efficiency since 1970[2,3]. They have been extensively used in a diverse range of consumer products including textiles, sofas, curtains, furniture, electric and electronic equipment, *etc*.[4,5]. However, growing body of studies reported that the persistent nature of PBDEs and their gradual leach out from consumer products into the environment cause global contamination[6].

PBDEs are considered as endocrine disrupting chemicals (EDCs) posing serious challenges to global environment and human health[3,7]. Multiple studies have reported that EDC exposure including PBDEs lead to thyroid dysfunction and other associated adverse health outcomes such as developmental abnormalities, reproductive outcomes *etc*.[8,9]. In context to our study, the PBDEs have a chemical structure quite like thyroid hormones, most notably thyroxine (T4)[10]. The thyroid hormones triiodothyronine (T3) and T4 are extremely important hormones of endocrine system. They regulate general body metabolism and promote development and differentiation of brain tissues and are essential for maintaining pregnancy[11]. Therefore, maintaining normal thyroid function is vital for psychological and physiological well-being[12] and is essential throughout the neurodevelopment in human beings[13,14]. Thyroxine binding globulin (TBG) is a carrier protein that binds to thyroid hormones, T3 and T4, and helps in their circulatory transport to the target tissues in the body. The other two transport proteins, transthyretin and serum

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albumin are also responsible for transporting thyroid hormones, but their role is minimal compared to TBG. Any interference in thyroid hormone binding to TBG is associated with altered serum thyroid hormone concentrations[15]. In our previous studies, we have reported the potential thyroid dysfunction by other PBDEs congeners[8,16]. However, studies on interference of PBDEs on thyroid hormone transport are limited, especially for the four PBDEs, i.e., BDE-28, BDE-85, BDE-154 and BDE-183. The structural studies on the indicated four PBDE ligands, against TBG ligand binding pocket have not been reported. Therefore, in this study, the ubiquitously detected environmental PBDEs, BDE-28, BDE-85, BDE-154 and BDE-183 were subjected to structural binding characterization against the ligand binding pocket of thyroxine transport protein, TBG. The molecular docking simulation approach was adopted to perform this study. Our study aimed to characterize the structural binding interactions of PDBEs with TBG and explore the thyroid transport disruption potential of the indicated commonly detected PBDEs.

Materials and Methods

The commonly detected PBDE ligands, BDE-28, BDE-85, BDE-154 and BDE-183 were chosen for this study. The coordinates for their three-dimensional structures were downloaded from PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/). Further, the structural binding characterization of all four PBDE ligands was performed using Schrodinger 2017 suite with Maestro 11.4 as graphical user interface (Schrodinger, LLC, New York, NY, 2017). The detailed methodology is described in our previous study[9,17].

Protein preparation

The three-dimensional structural coordinates for the TBG crystal structure in complex with native ligand, T4, solved at 1.55 Å resolution (PDB code: 4X30) was retrieved from Protein Data Bank (PDB; http://www.rcsb.org/). It was followed by processing where the protein complex was prepared for downstream steps using protein preparation wizard workflow of Schrodinger Glide for molecular simulation studies (Schrodinger suite 2017-4; Schrodinger, LLC) as described previously[9,17]. During the protein preparation step, the TBG crystal complex was first imported into Glide docking software. Further, hydrogen atoms and charges were added, and water molecules were also removed. Lastly, the hydrogen bond networks were optimized, and energy minimization was performed.

Ligand preparation

The structures of the four PBDEs, BDE-28, BDE-85, BDE-154 and BDE-183 were downloaded from PubChem compound database. The PubChem compound identity of BDE-28, BDE-85, BDE-154 and BDE-183 are 12110098, 177368, 15509898 and 15509899 respectively. Further, the two-dimensional structures of all the indicated ligands are presented in Fig. 1. The indicated ligands were prepared for simulation studies using LigPrep module of Schrodinger (Schrodinger 2017: LigPrep, Schrodinger, LLC) as discussed previously[9,17].

Induced fit docking

All the four PBDE ligands and T4 were docked in the TBG ligand binding pocket using Schrodinger′s Induced Fit Docking (IFD) module as described in our earlier studies[9,17]. The IFD is different from normal rigid docking as it induces flexibility in both the ligand as well as protein ligand binding site. We employed Schrodinger′s Glide and Refinement module in Prime to develop and validate the protocols to accurately predict the receptor ligand poses as well as the associated changes in the ligand binding pocket of the protein receptor. Concisely, the first step in performing the IFD was generating grid at TBG native ligand, T4 binding site. Then protein preparation step with

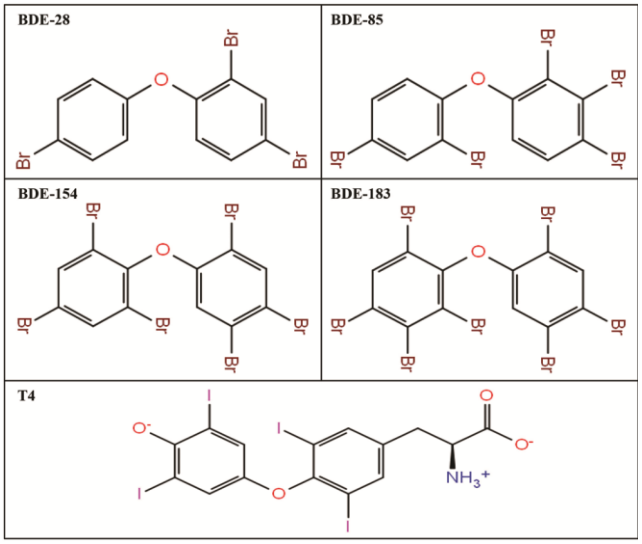

Fig. 1 — Two-dimensional structure of BDE-28, BDE-85, BDE-154, BDE-183 and TBG native ligand, T4.

RMSD cutoff of 0.18 Å was employed to perform the constrained minimization of protein receptor. Further, the initial Glide docking was performed using softened potential and optional side chain removal for all the PBDE ligands, and in total, twenty docking poses were retained by default. This was followed by side chain prediction for amino acids within 5 Å distance in each receptor-ligand complex for any pose and minimization was performed. In addition, ligand minimization was also performed for each complex (receptor-ligand) pose. We further performed Glide re-docking and IFD score estimation. Similarly, extended sampling protocol was also performed. Besides, the IFD was also performed for TBG native ligand, T4.

Binding affinity calculations

The molecular mechanics generalized born surface area (MMGB-SA) function of Prime module of Schrodinger 2017 was employed to calculate the binding affinity of all four indicated PBDE ligands against TBG binding pocket as described previously [9,17].

Results

The commonly detected PBDEs, BDE-28, BDE-85, BDE-154 and BDE-183, successfully docked in TBG ligand binding pocket. All four indicated PBDE ligands were placed tightly in ligand binding pocket using IFD approach, suggesting their stability in TBG ligand binding pocket. Although multiple display poses were produced for each protein-ligand docking complex, only the best ranking pose were finally chosen and carried forward for structural binding characterization and analysis. Likewise, the docking of TBG native ligand, T4 was successful and was stably placed in the ligand binding pocket following IFD. Again, the best ranking pose among the IFD docked poses of native ligand, T4 was selected and carried forward for further analysis. The best ranking docking display poses exhibiting TBG amino acid residue interactions with all the four PBDE ligands are shown (Fig. 2). Also, the best docking display pose exhibiting TBG amino acid residue interactions with TBG native ligand, T4, is also presented (Fig. 3). The PBDE ligands, BDE-28, BDE-154 and BDE-183 displayed interactions with 17 amino acid residues in the ligand binding pocket of TBG. The BDE-28 displayed interactions with 16 amino acid residues (Fig. 2A, 2B, 2C & 2D).

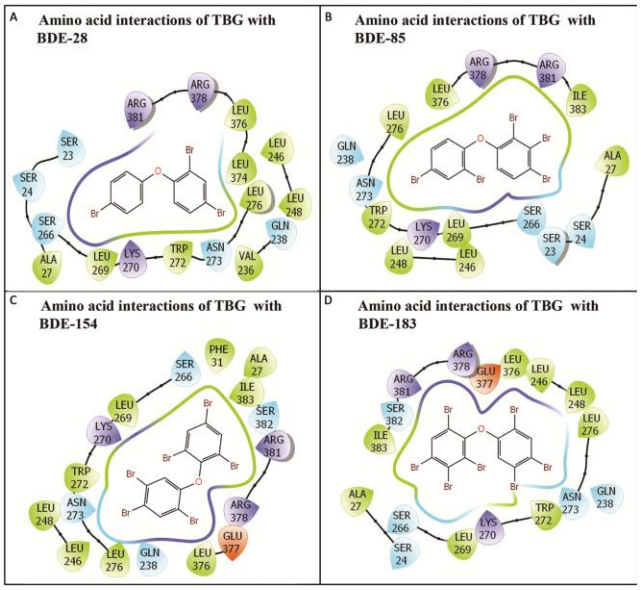

Fig. 2 — Molecular interactions of PBDEs (A) BDE-28, (B) BDE-85, (C) BDE-154, (D) BDE-183 with amino acid residues lining TBG ligand binding pocket.

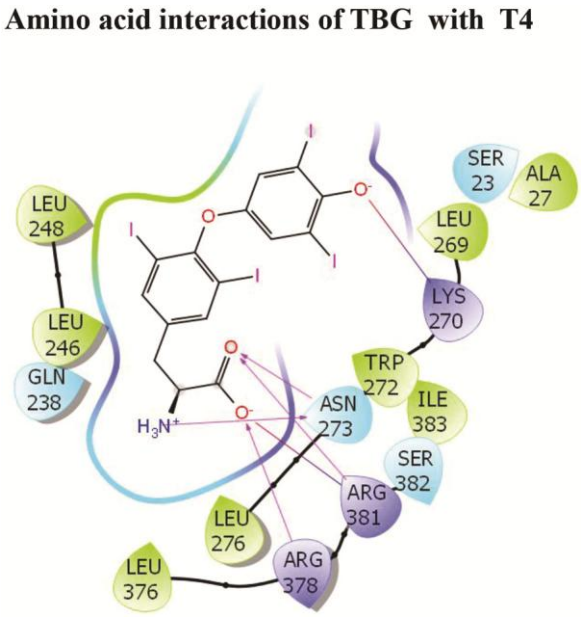

Fig. 3 — Molecular interactions of a TBG native ligand, T4 with amino acid residues lining TBG ligand binding pocket.

IFD of BDE-28 ligand with TBG

The IFD docking display complex TBG-BDE28 showed multiple interactions with numerous amino acid residues of TBG. Altogether, 17 amino acid residues showing different molecular interactions including hydrophobic, hydrogen bonding, van der Waals interactions *etc*. with BDE-28 were observed. The TBG ligand binding pocket amino

Table 1 — Structural binding indices of plasticizers (BDE-28, BDE-85, BDE-154, BDE-183) and a TBG native ligand, T4

Ligand	Number of interacting residues	Interacting residues common with native ligand (%)	IFD score	Docking score (Kcal/mol)	Glide score (Kcal/mol)	MMGB-SA (Kcal/mol)
BDE-28	17	86.6%	-828.80	-7.04	-7.04	-90.96
BDE-85	16	93.3%	-828.00	-7.12	-7.12	-98.48
BDE-154	17	93.3%	-829.46	-7.70	-7.70	-124.46
BDE-183	17	93.3%	-829.52	-6.94	-6.94	-126.26
T4	15	100%	-833.29	-8.37	-8.37	-124.31

acid residues engaged in multiple interactions were Ser-23, Ser-26, Ala-27, Val-236, Gln-238, Leu-246, Leu-248, Ser-266, Leu-269, Lys-270, Trp-272, Asn-273, Leu-276, Leu-374, Leu-376, Arg-378 and Arg-381 (Fig. 2A).

Similarly, the native ligand docking display complex, TBG-T4 showed multiple molecular interactions with numerous amino acid residues of TBG (Fig. 3). Altogether, 15 amino acid residues showing different molecular interactions including hydrophobic, hydrogen bonding, van der Waals, salt bridge interactions *etc*. with T4 were observed. These amino acids were Ser-23, Ala-27, Gln-238, Leu-246, Leu-248, Leu-269, Lys-270, Trp-272, Asn-273, Leu-276, Leu-376, Arg-378, Arg-381, Ser-382 and Ile-383. Furthermore, T4 also displayed two hydrogen bonding interactions with Asn-273. In addition, T4 also formed two more hydrogen bonding interactions each with Arg-381 and Arg-378. Besides, two salt bridge interactions each with Lys-270 and Arg-381 were also displayed (Fig. 3). Furthermore, other essential structural binding characterization parameters like IFD, Dock score, Glide score, binding energy *etc*. for BDE-28 as well as TBG native ligand, T4 are also presented (Table 1). Moreover, the commonality in TBG interacting amino acid residues between BDE-28 and T4 was estimated to be approximately 87%. The estimated binding energy which is extremely important for structural binding characterization for BDE-28 was low in comparison to TBG native ligand, T4.

IFD of BDE-85, BDE-154 and BDE-183 with TBG

The other three commonly detected PBDEs exhibited numerous molecular interactions with 16-17 amino acid residues. The docking display pose of BDE-85 exhibited 16 amino acid residues engaged in various molecular interactions with TBG (Fig. 2B). Further, the comparison between the docking poses of native ligand, T4 and BDE-85 revealed approximately 93% overlap in amino acid interactions. But other molecular interactions were also observed in TBG-BDE85 complex due to additional amino acid residues *i.e.* Ser-26 (Fig. 2B). Likewise, the TBG-BDE154 docking display pose exhibited 17 amino acid residues of TBG engaged in various molecular interactions (Fig. 2C). The comparison between the docking poses of native ligand, T4 and TBG-BDE154 revealed about 93% overlap in amino acid interactions. However, other molecular interactions were also observed in TBG-BDE154 complex due to additional amino acid residues *i.e.* Glu-377 (Fig. 2c). Similarly, the TBG-BDE183 docking display pose exhibited 17 amino acid residues of TBG engaged in various molecular interactions (Fig. 2D). The comparison between the docking poses of native ligand, T4 and TBG-BDE183 revealed approximately 93% overlap in amino acid interactions. However, several other molecular interactions were also observed in TBG-BDE183 complex due to additional amino acid residues i.e. Ser-24 and Glu-377 (Fig. 2D).

Discussion

This study was performed to enhance our understanding of potential TBG transport disruption and subsequent thyroid dysfunction by commonly used PBDE, BDE-28, BDE-85, BDE-154 and BDE-183. The detailed result analysis indicated the successful and stable binding of all the PBDE ligands in TBG ligand binding pocket. In addition, the estimated structural binding parameters such as IFD score, Glide score, Dock score and the binding energy values also suggested the good quality and stability of TBG-ligand complexes. Further, various molecular level interactions such as hydrogen bond, pi-pi interactions, salt bridge, *etc.*, observed in TBG-ligand complexes play a key role in the stability of these complexes. The comparison of the chosen docking pose of TBG native ligand, T4, with all the indicated PBDE ligand complexes revealed 86-93% overlap in the interacting amino acid residues in the TBG ligand

binding pocket. Besides, the estimated binding energy values for BDE-154 and BDE-183 ligands were very close to the values calculated for TBG native ligand, T4. However, the values calculated for the remaining two PBDEs, BDE-28 and BDE-85 were lower than TBG native ligand, T4. Therefore, the results of this study suggest that the indicated PBDEs, especially BDE-154 and BDE-183 have potential to disrupt the TBG transport which might subsequently cause thyroid dysfunction.

Very limited studies are available on structural binding characterization of TBG with PBDEs. Besides, the structural studies on TBG interactions with above indicated all four PBDE ligands, BDE-28, BDE-85, BDE-154 and BDE-183 are not reported. However, our recent study reported the molecular interactions and structural characterization of TBG with another PDBE ligand, BDE-153[8]. We also reported the binding of hydroxy and methoxy metabolites of PBDE with TBG[9]. In another recent study, the PBDE sulfate metabolites were reported to bind with TBG suggesting potential thyroid dysfunction[18]. An *in vitro* fluorescence probe based binding study demonstrated that various hydroxylated PBDEs bound with TBG. Further, some of the analogues show stronger binding than T4[19]. A study using fluorescence displacement assay suggested the potential for hydroxylated PBDEs to displace thyroid hormones from TBG binding sites[20]. A surface plasmon resonance study also reported that hydroxylated metabolites of some PBDEs (BDE-47, BDE-49 and BDE-99) showed high binding with TBG[21].

Besides, several epidemiological studies have reported an association between the PBDE exposure and altered thyroid levels. A study conducted on pregnant (past 34 weeks) women reported positive association between the maternal serum concentrations of BDEs-47, -99, -100 and elevated levels of free T4 (FT4) and total T3 (TT3)[22]. According to HOME (Health Outcomes and Measures of the Environment) study conducted in the second trimester of pregnancy, the increased T3 and T4 levels displayed association with maternal serum levels of BDE-28 and BDE-47. This study also revealed a significant trend between the maternal levels of BDE-47 and total T4 (TT4)[23] in the third trimester. In addition, a significant correlation was observed between the TT4 and BDE-153 from Wenling residents in China[24]. Furthermore, numerous studies reported the association between the PBDE exposure and adverse effects on various developmental parameters. For example, prenatal PBDE exposure was associated with slower psychomotor and cognitive development[25] and lower levels of language and social development[26] in infancy and toddlerhood. Likewise, prenatal PBDE exposure is associated with poorer fine motor skills at preschool and school age[27]. Moreover, lower intelligence quotients (IQ) and neurodevelopmental problems are also associated with prenatal PBDE exposure[25,28] at cognitive level. The other problems observed at cognitive level are lower executive function[23] and attentional abilities[27,29], which also indicate potential changes in neurodevelopment. The studies on preschool and school age children in the United States suggested a negative association between prenatal PBDE exposure and motor, behavioral, and cognitive outcomes[30].

Additionally, several studies on animal models have also reported that PBDE exposure is associated with altered thyroid hormone levels. For example, a 90-day long study on rats administered with BDE-71 in diet reported decrease in T4 concentrations without any impact on T3 levels (IPCS, 1994). A mice study reported a decrease in T4 levels on exposure to various concentrations of BDE-71 for 14 days[31]. Likewise, another mice study reported a decrease in total plasma T4 levels by 31% on exposure to BDE-47 for 14 days[32]. Similarly, the decrease in both free as well as total plasma T4 levels in female rats following 14 days BDE-47 exposure was reported. However, no effect was observed in TSH levels[33]. Further, BDE-71 exposure resulted in decrease in serum T4 levels in dams as well as in offsprings both during and after the gestation period[34]. BDE-71 was reported to reduce serum T4 levels in adult rats, but TSH levels were unaffected. Furthermore, the rat offspring perinatally exposed to BDE-71 also reported the reduced serum T4 levels with no effects on TSH levels[35]. A thyroid hyperplasia was reported in adult rats on 30 days long exposure to deca and octa-BDE mixtures[36]. Another study reported that maternal exposure to halogenated diphenyl ethers decreased T4 levels, during gestational period in dams and pre-weaning offsprings. However, the T3 or TSH levels were not disturbed either in dams or in offsprings[37]. Likewise, similar results were reported on exposure to other congeners such as BDE-47[38,39], BDE-99[40], and BDE-153[41]. Similarly, a study conducted on rats indicated that T3 levels were reduced but TSH levels

were increased on exposure to BDE-209[42]. Various studies on animal models have indicated that prenatal PBDE exposure has adverse effects on neurodevelopment. For example, exposure to BDE-209 was suggested to disrupt cholinergic receptor response which is closely associated with cognitive and behavioral functioning and impaired memory and learning[43,44].

Conclusion

The results of our study revealed that the four PBDE ligands, BDE-28, BDE-85, BDE-154 and BDE-183 displayed a high percentage of commonality in interacting amino acid residues in TBG ligand binding pocket with that of TBG native ligand, T4. Furthermore, among the indicated four PBDEs, the estimated binding energy values for BDE-154 and BDE-183 were similar and approximately equal to that of TBG native ligand, T4. However, the values calculated for the remaining two ligands, BDE-28 and BDE-85 are lower compared to the values for TBG native ligand, T4. Therefore, on a preliminary basis, our results suggested that BDE-154 and BDE-183 and to a lesser extent BDE-28 and BDE-85 have the potential for competitive binding to TBG against native ligand T4. Taken together, this potential interference in the binding of T4 to TBG may lead to dysregulation of thyroid hormone transport in blood stream culminating in thyroid hormone dysfunction and implications for thyroid associated health outcomes

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Conflict of interest

The authors acknowledge that there is no conflict to declare.

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