

It's a Wonderful Metabo(life): The Story of Estrogen Sulfotransferase

Saint Thomas More SMART Team: Anna Bollis, Ben Boren, Faith Bowman, Robyn Cabigting, Bradley Drew, Gabriella Hamilton, Kelly Howell, Martha Lezama, Sophia Olmos, Matt Peter, Carolyn Sikora, and Megan Wengelewski



CONCORDIA
UNIVERSITY
WISCONSIN

Advisor: Kathy Stelling

Mentors: Joseph McGraw, Ph.D. & Cameron Patterson, Doctor of Pharmacy Candidate, Concordia University Wisconsin School of Pharmacy

I. Abstract

Hypoplastic Left Heart Syndrome (HLHS) is a disorder of the fetal heart in which the ventricles and aorta are formed improperly. As a result, infants with this condition will die shortly after birth unless they receive immediate surgery. According to the World Health Organization, this syndrome affects about 1 in every 4,300 babies born in the United States each year. Dr. Joseph McGraw and Dr. Andrew Pelech are studying whether this condition could be linked to brominated flame retardants, or BFRs. BFRs are a class of chemicals that have bromine atoms attached to them in a specific sequence. Estrogen sulfotransferase (EST) is a metabolic enzyme that metabolizes various fatty acids, neurotransmitters, and hormones. The Saint Thomas More SMART (Students Modeling A Research Topic) Team modeled EST using 3D printing technology to further investigate the structure-function relationship. One function of EST is to attach a sulfate group to thyroid hormone, thyroxine, or estrogen. This process changes the hormones from non-polar to more polar substances. The polar form of thyroxine may be absorbed into the fetus and later metabolized back to the thyroid hormone for use in fetal organ development. BFRs can closely mimic hormones by competing for various enzymes and transporters involved in hormone regulation. However, BFRs do not function in the same way as hormones such as thyroxine. BFRs can disrupt normal thyroid hormone metabolism by inhibiting enzymes such as EST during critical times of fetal development. Further research may result in new avenues for effective treatment of fetal developmental disorders such as HLHS..

II. EST and Birth Defects

Researchers have pondered over the effects that one's environment can have on peoples' health status. A recent cohort study of pregnant African American women in the Chicago area consuming Great Lake fish showed an increase in adverse birth outcomes, such as low birth weight. Compared to other major cities, Chicago participants carried a high level of polychlorinated biphenyl (PCBs) which are also found in fish. The women that demonstrated higher levels of PCBs relative to PCB metabolites gave birth to children with low birth weight. PCBs and polybrominated diphenyl ethers (PBDEs) are both found in the environment and contain biphenyl rings. PCBs have been declining in the environment while PBDEs were rising in the environment until recently. The PCB ring contains chlorine and PBDEs contain bromine on their rings. Bromine is found in many materials because of brominated flame retardants or BFRs. An extreme elevation of PBDEs in a mother and her child who had HLHS has spurred study of the relationship between PBDEs and HLHS. (See figure 1) PCBs and PBDEs both mimic the structure of thyroid hormone (TH). Thyroid hormone is needed by the fetus for organ development. The fetus is able to take in TH that has been sulfated by estrogen sulfotransferase. The metabolites of PBDEs block estrogen sulfotransferase and block thyroid hormone and estrogen sulfation.

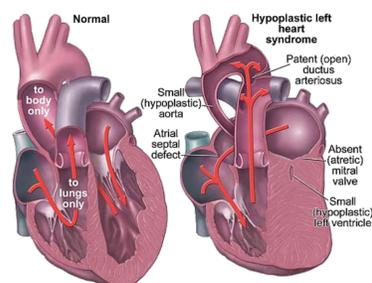
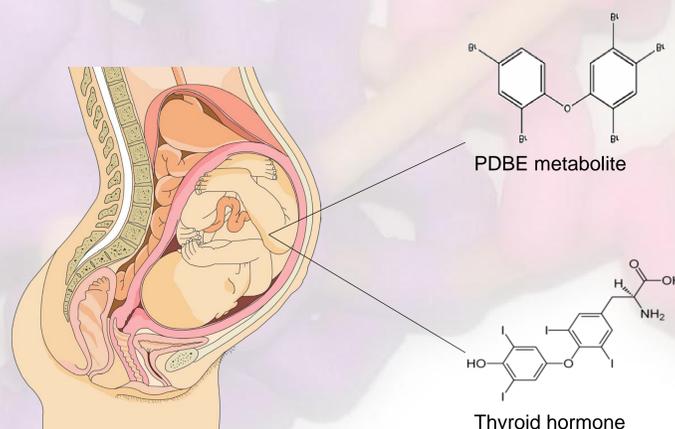


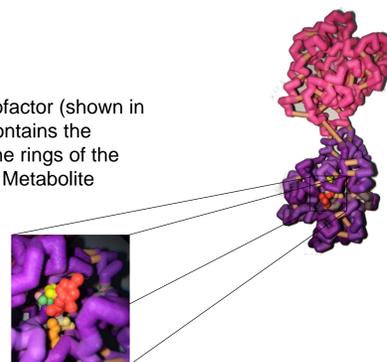
Figure 1: Comparison of normal heart to a hypoplastic left heart¹

III. Ligand Binding to EST

It is necessary to compare EST's interaction with PBDEs and their metabolites versus its reaction with thyroid hormone and estrogen. Calculations were performed to measure ligand binding to estrogen sulfotransferase. The molecular structures of each ligand were downloaded using the 4JVN pdb file, thus creating the model of estrogen sulfotransferase by deleting all of the ligands that were already bound to it. Next, the AutoDock software was used to bind each ligand with estrogen sulfotransferase (EST). After inputting the parameters for the binding of the ligands with EST, AutoDock automatically calculates where the ligand is most likely to bind, and generates a table of binding energies for the various binding states of the ligand with the protein. (see data table to the right)



The cofactor (shown in red) contains the bromine rings of the PBDE Metabolite



Lysine 47 (shown in green) is an amino acid that interacts with serine 137 to stop the sulfate group from attaching to the active site

The EST active site (shown in yellow) is composed of lysine, phenylalanine, and histidine that allows the thyroid hormone to enter the fetal compartment

IV. Results

The charts below are the result of computer modeling of ligand binding to estrogen sulfotransferase. This chart shows us that estradiol binds with a very similar binding energy as 3OH-PBDE47. By comparing the relative binding we can identify how well the contaminant (3OH-PBDE47) can compete with estrogen for EST binding.

3OH-PBDE47 & Estrogen Sulfotransferase Clustering Histogram

Cluster Rank	Lowest Binding Energy	Run	Mean Binding Energy	Number in Cluster
1	-8.04	33	-7.61	21
2	-7.36	38	-7.14	10
3	-7.32	34	-6.93	13
4	-6.71	64	-5.98	14
5	-6.58	86	-6.47	4
6	-6.07	56	-5.67	4
7	-6.06	66	-6.03	3
8	-5.88	45	-5.70	13

Estradiol & Estrogen Sulfotransferase Clustering Histogram

Cluster Rank	Lowest Binding Energy	Run	Mean Binding Energy	Number in Cluster
1	-7.99	20	-7.99	2
2	-7.01	62	-6.93	20
3	-6.80	98	-6.77	30
4	-6.80	77	-6.73	17
5	-6.64	89	-6.63	4
6	-6.62	43	-6.55	7
7	-6.52	68	-6.52	3
8	-6.03	92	-5.96	7

V. Significance

The metabolites of the PBDEs contain a biphenyl ring similar to the thyroid hormone which allows it to attach to estrogen sulfotransferase. Due to the widespread use of flame retardants in all materials and objects today, the PBDEs can pose harm to some individuals. People who have difficulty ridding their bodies of PBDEs and their metabolites can flood their system with more contaminants than thyroid hormone. Therefore, the ratio of contaminants to thyroid hormone is severely unbalanced, allowing the contaminants to attach to estrogen sulfotransferase and disrupt normal hormone transport into the fetal tissues.

References

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