TRANSTHYRETIN (TTR): CARRIER OF THYROXINE AND IT’S EVIL TWIN (ENVIRONMENTAL POLLUTANTS)

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ABSTRACT

Transthyretin (TTR) is a carrier protein in the blood that binds to and transports the thyroid hormone thyroxine throughout the human body. The thyroid hormone is necessary for fetal development and metabolism regulation. TTR is a tetramer formed from two dimers. Ala-108, Ser-117, Thr-119, Lys-15, Leu-17, Thr-106, and Val-121 all play a role in binding the thyroxine in a hydrophobic channel formed where the two dimers come together. Polymethylated diphenyl ethers (PBDEs), found in flame retardants, which are in numerous household products, are converted in the body to hydroxy-PBDEs. Hydroxy-PBDEs mimic the shape of thyroid hormones allowing them to bind with TTR. Hydroxy-PBDEs can have a stronger affinity to bind to TTR, disrupting the transport of the thyroid hormone necessary for developmental and metabolic processes. An initial study shows a possible correlation between high levels of PBDEs and hypoplastic left-heart syndrome, a condition found in four out of 10,000 newborns (Lucile Packard Children’s Hospital at Stanford) in which the left side of the heart does not fully develop. Wauwatosa West SMART Team (Students Modeling A Research Topic) modeled TTR using 3D printing technology.

THYROXINE: THE THYROID HORMONE

• Plays a part in the development of the brain, skeleton, heart, and other organs
• Hyperthyroidism (too much thyroxine) causes weight loss, diarrhea, racing heart, and irritability
• Hypothyroidism (too little thyroxine) causes weight gain, sluggishness, slow heart rate, low body temperature, and low blood pressure
• Deficiencies in thyroid hormone concentrations before birth and shortly after birth negatively affects the heart rate, growth, hearing, motor control, and intelligence

POLYBROMINATED DIPHENYL ETHERS (PBDEs)

• Environmental toxins in flame retardants
• Commonly added to household products such as furniture, clothing, electronics, cars, walls
• Exposure due to consumption of food and respiration
• Levels risen significantly in the United States over the past two decades
• Milwaukee has high concentrations
• Once absorbed in the body and metabolized, stored in lipids, found in blood, and breast milk
• Metabolites structurally similar to thyroxine, allow binding to TTR
• Some Hydroxy-PBDE congeners bind more strongly to TTR than thyroxine
• Has been shown to disrupt thyroid hormone transport throughout the body
• Certain forms have been banned in Europe since 2004
• PBDEs, banned industrial chemicals, structurally similar to PBDEs and thyroxine
• PBDEs shown to have negative influence on thyroid function

CONCLUSION

Transthyretin might be a component in causing birth defects, which could include hypoplastic left heart syndrome (HLHS). As previously stated, one mother-infant pair showed unusually high levels of PBDEs. This data was collected from eight mothers and infants with HLHS. More research is needed to determine if there is a correlation between this heart defect and PBDEs. Transthyretin could play a role in this process. This data may disrupt normal thyroid hormone circulation by displacing thyroxine in the TTR-thyroxine complex. This data is inconclusive and suggests further investigation.

HYPOPLASTIC LEFT HEART SYNDROME

• Left ventricle misshapen and significantly smaller from birth
• Heart not capable of pumping blood efficiently through the body
• Condition fatal without treatment
• Cause of hypoplastic left heart syndrome unknown

Dr. Pelech and Dr. Dellinger studied environmental contaminant serum concentrations in eight infants diagnosed with hypoplastic left heart syndrome (HLHS). Based on these results, Dr. Joseph McGraw and his colleagues are currently investigating a possible correlation between HLHS and high levels of PBDEs in mother infant pairs. High levels of PBDEs were found in one mother-infant pair (shown below).

Comparison Between Concentrations of PBDEs in Breast Milk from North America and Europe

PBDE 47 19.6 (16.4-23.5) 195 (102-239) 166.2 394.1
PBDE 99 3.72 (3.15-4.40) 33.3 (23.3-46.0) 34.9 117.0
PBDE153 4.78 (4.20-5.43) 54.5 (34.6-62.9) 38.7 58.8

Averaage PBDE concentrations from the National Health and Nutrition Examination Survey compared to data from the Wisconsin Pediatric Cardiac Birth Defects Registry

PCBs, banned industrial chemicals, structurally similar to PDBEs and thyroxine

• Deficiencies in thyroid hormone concentrations before birth and shortly after birth negatively affects the heart rate, growth, hearing, motor control, and intelligence

TRANSTHYRETIN: THYROXINE CARRIER

• Tetramer from two dimers
• Hydrophobic channel with four binding sites

TTR-thyroxine complex

The SMART Team Program (Students Modeling A Research Topic) is funded by a grant from NIH-SEPA 1R25OD010505-01 from NIH-CTSA UL1RR031973.