

TRANSLATIONAL RESEARCH ON THE ROLE OF DEVELOPMENTAL PESTICIDE EXPOSURE AND ADHD

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ADHD

- 8-12% of Children Affected in U.S.
- Males Gender Preference
- Hyperactivity
- Impulsivity
- Attention Deficits
 - Predominantly Inattentive
 - Hyperactive-Impulsive
 - Combined
- ADHD is a Complex Spectrum Disorde
 - Variable Symptoms
 - Variable Response to Therapeutic
 - Numerous Co-Morbid Conditions





MULTIPLE CONTRIBUTORS TO ADHD





GENETIC CONTRIBUTION TO ADHD





Faraone and Larsson, 2019

Environmental Factors in ADHD

- Low Birth Weight
- Hypoxia
- Maternal Smoking?
- Lead
- PCBs?
- Methyl Mercury?
- Pesticides?



Why Pesticides?

- Specifically put into the environment
- Target and non-target species affected
- Children are thought to be uniquely susceptible
 - Child-specific behaviors
 - Immature detoxication system
 - Critical periods of neuronal development





Experimental Design





Behavior Neurochemistry Molecular Markers



Richardson et al., 2015

DEVELOPMENTAL DELTAMETHRIN EXPOSURE CAUSES HYPERACTIVITY







Richardson et al., 2015

Operant Behavioral Tasks



INCREASED FIXED INTERVAL RESPONSE IS INDICATIVE OF IMPULSIVENESS IN CHILDREN WITH ADHD





Sagvolden

DELTAMETHRIN INCREASES FI RESPONSES: EVIDENCE FOR IMPULSIVE-LIKE BEHAVIOR

Male Resp. Data

Female Resp. Data



DELTAMETHRIN INCREASES FR RESETS AND DECREASES MEAN LONG WAIT IN MALES





PYRETHROID EXPOSURE IS ASSOCIATED WITH INCREASED RISK OF ADHD DIAGNOSIS

Variable	Sample Size (n)	Adjusted Odds Ratio (95% CI)	<i>p</i> - value
Total	2,123		
Age (years)	2,123	1.1 (1.0-1.2)	0.162
Sex			
Female	1,121	Referent	
Male	1,002	2.9 (1.5-5.7)	0.003
Race			
Non-Hispanic white	702	Referent	
Other Hispanic	98	0.4 (0.1-1.3)	0.138
Mexican American	559	0.3 (0.1-0.5)	<0.001
Non-Hispanic black	106	0.6 (0.4-0.9)	0.019
Other, including multiracial	658	0.6 (0.1-3.0)	0.557
Covered by health			
insurance			
No	394	Referent	
Yes	1,729	1.3 (0.6-2.9)	0.545
3-PBA quintiles (μg/l)			
1 st quintile (0.07-0.07)	482	Referent	
2 nd quintile (0.1-0.23)	385	3.5 (1.7-7.3)	0.001
3 rd quintile (0.24-0.45)	408	1.6 (0.9-3.0)	0.119
4 th quintile (0.46-1.1)	431	2.1 (0.9-4.9)	0.068
5 th quintile (1.11-462.1)	417	2.1 (1.04-4.2)	0.037
3-PBA Above the LOD			
(0.1 µg/l)			
No	482	Referent	
Yes	1,641	2.3 (1.4-3.9)	0.002



Richardson et al., 2015

SYMPTOM COUNTS FROM DISC ANALYSIS REPRODUCE EFFECTS OBSERVED IN MICE

	Inattentive Symptom Count	Hyperactive-Impulsive Symptom Count
	ACR (95 % CI)	ACR (95 % CI)
Urinary 3-PBA Level ≥ LOD		
Overall	1.26 (0.75, 2.12)	1.77 (0.95, 3.30)
Boys	1.61 (0.92, 2.80)	2.49 (1.17, 5.27)
Girls	0.89 (0.44, 1.81)	1.01 (0.51, 2.00)
Log10-transformed Urinary 3-PBA		
Overall	1.21 (0.83, 1.78)	1.50 (1.03, 2.19)
Boys	1.49 (1.05, 2.12)	1.57 (1.05, 2.34)
Girls	1.00 (0.58, 1.71)	1.51 (0.88, 2.60)

Abbreviations: 3-PBA, 3-phenoxybenzoic acid; ACR, Adjusted Count Ratios; LOD, limit of detection

^aAdjusted for child's age, race/ethnicity, income, health insurance status, prenatal tobacco exposure, blood lead level (\log_{10} -transformed), urinary organophosphate metabolite level (\log_{10} -transformed), and urinary creatinine level. Overall models also adjust for sex



DOPAMINE SYSTEM AND ADHD





D1 RECEPTOR CONTRIBUTES TO BEHAVIORAL DYSFUNCTION





DEVELOPMENTAL DELTAMETHRIN INCREASES D1 RECEPTORS





Richardson et al., 2015

LONG-TERM INCREASES IN DAT AND D1 MRNA EXPRESSION





DELTAMETHRIN DECREASES EXPRESSION OF DNMTS





KNOCKDOWN OF DNMTS INCREASES DRD1





Green et al., 2015 Unpublished data

DEVELOPMENTAL DELTAMETHRIN CAUSES HYPOMETHYLATION OF DRD1





ARE THERE CRITICAL PERIODS OF EXPOSURE?

- Gestational-Lactational
 - Hyperactivity
 - Impulsive Behavior
 - Dopamine system appears to be primary target
 - Epigenetic mechanisms
 - NHANES data supportive of animal work
- Postnatal (unpublished data)
 - Hyperactivity
 - Impulsive Behavior
 - Learning and memory?
 - Dopamine system and hippocampus both appear to be targeted

- Adult
 - ER Stress (Hossain and Richardson, 2011; 2020; Hossain et al., 2015; 2019)
 - Learning and memory deficits (Hossain et al., 2015; submitted)
 - Effects on adult neurogenesis (Hossain et al., 2015; submitted)
 - No hyperactivity
 - Hippocampus appears to be a sensitive target
 - Human studies needed



CONCLUSIONS

- Pyrethroid Exposure is Associated with ADHD Risk, Particularly in males
- Developmental Deltamethrin Reproduces Features of ADHD
 - Hyperactivity
 - Impulsive-like Behavior
 - Male Sex Bias
- Dysregulation of the DAT and Drd1 Contribute to Behavioral Dysfunction
- Epigenetic Mechanisms are Responsible for the Long-Term Changes in DAT and DRD1



OPPORTUNITIES AND CHALLENGES

- Who is at risk, when and why?
- How to promote and support multidisciplinary research teams
- How to develop and use methodology to address polygenic and multiple environmental contributors
- Harnessing new technologies (i.e. CRISPR) to generate relevant animal models for testing GxE Interactions
- Laboratory models need to be validated for the disease of interest
- How to leverage existing and ongoing neuroscience studies to incorporate environmental exposure assessment
- How to determine the relevance of peripheral biomarkers to changes in the brain

