Global Environmental Health

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How May Environmental Factors Impact Potential Mechanisms in Humans?

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Autism is a Complex Disorder

Multiple genes are involved in conferring autism susceptibility
Scope of the Problem

• ~4,000,000 births per year in U.S.

• ~ 120,000 major defects reported for live-born infants
  - structural defects (neural tube, heart)
  - growth retardation
  - functional deficits

• Underestimate: most neurological and behavioral problems are not diagnosed until early childhood or young adulthood

• At present, the causes of the majority of developmental defects are not understood.

• ~ 3% of all developmental defects are attributable to exposure to toxic chemicals
  ~ 25% of all developmental defects may be due to a combination of genetic and environmental factors.
What we don’t know about environmental triggers ----quite a bit!

>53,000 commercially important chemicals

- *NTP* survey of 49,000 industrial chemicals
  ~80% lack adequate toxicity data (especially DNT)

- 3,400 pesticides are more heavily regulated
  ~64% lack adequate data for risk assessment

- 3,400 cosmetic ingredients
  ~74% lack adequate data for risk assessment

- 8,600 food additives
  ~80 % lack adequate data for risk assessment

*National Toxicology Program Report (1992)*
Toxcast™ Program
Prioritizing Toxicity Testing of Environmental Chemicals

Little is known about:
- Additivity
- Synergism
- Antagonism
- Relative timing
Autism is a multi-system disorder whose outcome is likely to be more profoundly impacted by environment than other disorders and diseases.

What are the possible mechanisms involved?
Log Toxicant Concentration

% with adverse effects

Autism

Typical

TD_{50}

Log Toxicant Concentration
Framework for understanding gene-environment interactions impacting autism risk

Hypothesis generating concept:

Genetic susceptibilities $\times$ environmental exposures $\times$ timing = prevalence and severity of developmental disorders
Mutations within Ca\textsuperscript{2+} channels are associated with autism susceptibility

Timothy Syndrome

Cell, Vol 119, 19-31, 1 October 2004

Ca\textsubscript{v}1.2 Calcium Channel Dysfunction Causes a Multisystem Disorder Including Arrhythmia and Autism

Defective/deficient GABAa Receptors in Autisms

- Epigenetic mechanisms
  MeCP2-deficiency associated with down regulation of GABRβ3

- Complex gene-gene interactions
  Polymorphisms at GABRα4 are involved in the etiology of autism,
  interaction with GABRβ1 increases autism risk
  (Ma et al, 2005, Am J Hum Gen 77, 377)

- Polymorphisms
  GABRγ1, GABRβ3 genes...

Pesticides (Chlorinated hydrocarbons block GABAa receptors)
PCBs alter the balance of excitation and inhibition in the developing brain
Pesticides that block the pore GABA<sub>A</sub> receptors

Chlorinated hydrocarbon pore blockers

- Lindane (head lice, scabies)
- Hepatchlor (1988)
- Chlordane (1988)
- Dieldrin (1987)
- Kepone (1978)
- Toxaphene (1990)

To appreciate the effectiveness of these materials as termiticides, consider that wood and wooden structures treated with chlordane, aldrin, and dieldrin in the year of their development are still protected from damage--more than 55 years!
Pesticides that antagonize GABAa Receptors

Non-Competitive GABA antagonist:

Fipronil (4-alkyl-1-phenylpyrazole)
  >800 tons applied in 2000
  Regent®
  Goliath®
  Nexa®
  Adonis®
  Chipco Choice®
  Frontline®

“Structure-activity studies described here reveal that fipronil retains its very high binding potency at the human beta3 and house fly gamma-aminobutyric acid (GABA) receptors”

GABA receptor antagonists and insecticides: common structural features of 4-alkyl-1-phenylpyrazoles and 4-alkyl-1-phenyltrioxabicyclooctanes
Sammelson RE, Caboni P, Durkin KA, Casida JE
Gene-Environment interactions altering the balance of excitatory and inhibitory circuits

Model of autism: increased ratio of excitation/inhibition in key neural systems

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Normal receptive field within primary auditory cortex (PN35-50)

Perinatal 2,2,3,5′6'-pentachlorobiphenyl

Framework for Future Studies

Mechanistic approaches are needed to understand gene-environment interactions in autism susceptibility.

Diagram:
- Genetic susceptibility
- Environmental "Factors"
- Repair
  - Impaired DNA Methylation
- 'Normal' phenotype
- Autism Severity
Framework for Future Studies

Mechanistic approaches are needed to understand gene-environment interactions in autism susceptibility

Environmental “Factors”
- Competitive & Noncompetitive GABR Blockers
- Alteration of cell signals: PCBs, PBDEs, PCDEs

Genetic susceptibility
- GABR deficiency
- Ca²⁺ channels

Repair
- Impaired DNA Methylation

‘Normal’ phenotype

Autism Severity
Framework for Future Studies
What We Need

Humans

Case-Control Epidemiologic studies that are designed with the power to identify gene-environment interactions

Studies investigating immunological susceptibilities

Studies investigating nutrition and autism

Molecular, cellular, and *in vivo* models

Mechanistic and behavioral studies that use low [subtoxic] focus on signaling systems known to be affected in autism

Redirect focus to environmentally important chemicals that lack or have poor dioxin-like activity

Studies that focus on immune-neurodevelopment connection

Nutrition-based models