Neuromuscular systems as a convergent target of environmental stress in Ocean and Human Health

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Chemicals and Neurodevelopmental Disorders

- Persistent Organic Pollutant exposure correlates with neurodevelopmental deficits

  *Example:* Pre and post-natal exposure to PCBs associated with lower IQ, attention deficit disorder, and motor impairments

- Of the 209 congeners, *ortho* PCBs are known to target important neuronal pathways

PCBs found in plastics washed on to the world's beaches (ng/g-pellet; pelletwatch.org)
Ryanodine Receptor as a Molecular Target

Important for proper

- Neuronal health and development
- Cardiac and skeletal muscle physiology, contractility, health
- Endocrine signaling

Alterations associated w/

- Cardiac arrhythmias, failure
- Skeletal muscle myopathies
- Altered neuronal signaling and potential contribution to neuronal degeneration
Importance of Structure at the RyR

RyR-related Toxic Outcomes

PCBs, PBDEs or their metabolites

- **Neurotoxicity**
  - Increased neuronal activity
  - Altered neuronal growth and morphology
  - Altered synaptic and network connectivity

- **Muscle Toxicity**
  - Altered excitation-contraction coupling
  - Altered expression of crucial muscle proteins

Triclosan

- Reduced cardiac output
- Reduced skeletal muscle contractility
- Decreased muscle strength (mice) and swimming performance (fish)
RyR Toxicity and Ocean and Human Health

PCB Congener Chlorine substitution

Pessah et al., (2006)
Hwang et al., (2006)
Kostyniak et al.(2005)
DeCaprio et al..(2005)

Ryanodine Receptor Activity (EC_{2x} (µM))

Percent of Total PCB

Richmond, CA Sediments Σ= 50.3%

Fox River Fish Σ= 52.3%

Akwasasne Mohawks Serum Σ= 44.9%

(+90)
(+24)
(+123)
Other Compounds (ex. Triclosan)

Potential drinking water contaminant

Urinary Concentrations of Triclosan in the U.S. Population: 2003–2004
Antonia M. Calafat, Xiaoyun Ye, Lee-Yang Wong, John A. Reidy, and Larry L. Needham

Triclosan persistence through wastewater treatment plants and its potential toxic effects on river biofilms
Marta Ricart\textsuperscript{a,b,*}, Helena Guasch\textsuperscript{b}, Mireia Alberch\textsuperscript{c}, Damià Barceló\textsuperscript{a,d}, Chloé Bonnineau\textsuperscript{b}, Anita Geiszinger\textsuperscript{b}, Marinel la Farré\textsuperscript{d}, Josep Ferrer\textsuperscript{c}, Francesco Ricciardi\textsuperscript{b}, Anna M. Romani\textsuperscript{b}, Soizic Morin\textsuperscript{e}, Lorenzo Proia\textsuperscript{b}, Lluís Sala\textsuperscript{f}, David Sureda\textsuperscript{c}, Sergi Sabater\textsuperscript{a,b}

Temporal trends of triclosan contamination in dated sediment cores from four urbanized estuaries: Evidence of preservation and accumulation
Mark G. Cantwell\textsuperscript{a,*}, Brittan A. Wilson\textsuperscript{b}, Jun Zhu\textsuperscript{c}, Gordon T. Wallace\textsuperscript{c}, John W. King\textsuperscript{d}, Curtis R. Olsen\textsuperscript{c}, Robert M. Burgess\textsuperscript{d}, Joseph P. Smith\textsuperscript{e}

Occurrence of triclosan in plasma of wild Atlantic bottlenose dolphins (\textit{Tursiops truncatus}) and in their environment
Patricia A. Fair\textsuperscript{a,*}, Hing-Biu Lee\textsuperscript{b}, Jeff Adams\textsuperscript{a}, Colin Darling\textsuperscript{b}, Grazina Pacepavicius\textsuperscript{b}, Mehran Alaee\textsuperscript{b}, Gregory D. Bossart\textsuperscript{c,1}, Natasha Henry\textsuperscript{a}, Derek Muir\textsuperscript{b}
Understanding Complex Etiologies

Environmental stressor(s)

Epigenetics

Genetics

Development
Mixtures at the RyR

(A) Activity of non-coplanar compounds (PCBs and PBDEs) are additive at the receptor

(B) NDL PCB mixtures currently detected in fish tissue activate the receptor

Fritsch and Pessah. 2013
Environmental Stress X Genetic Disorders?

**RyR x Heart**
- Heart Failure
- Arrhythmias (CPVT; ARVD2; TS)
- Sympathetic Dysregulation
- Ischemic Injury
- Cardiomyopathies

**RyR x skeletal muscle**
- Malignant Hyperthermia
- Central Core Disease
- Heat Stress
- Aging related weakness
- Myopathies (MG, MD…)

**RyR x Brain**
- Alzheimer’s Disease
- Parkinson’s Disease
- Anxiety disorders

**RyR x Endocrine**
- Metabolic Syn/Type1&2 Diabetes
- Pituitary hormone secretion
- GPER signaling (estrogen signaling)
- AR signaling (androgen signaling)

**RyR x Immune**
- Dendritic cell activation
- T cell activation (HIV)
Combined genetic and chemical associations?

(ex) PCB Levels and 15q forms of Autism

(Mitchell et al., 2012)
Looking Forward

• Define sensitive species, individuals and developmental stages

• Combined effects of multiple stressors
  – Similar mechanisms
  – Convergent molecular or physiological systems
  – Changing environmental factors (heat+chemical)

• Long-term population impacts
  – Pollutants affecting Ocean and Human Health have now spanned multiple “generations”
  – Little information regarding contribution to disease incidence