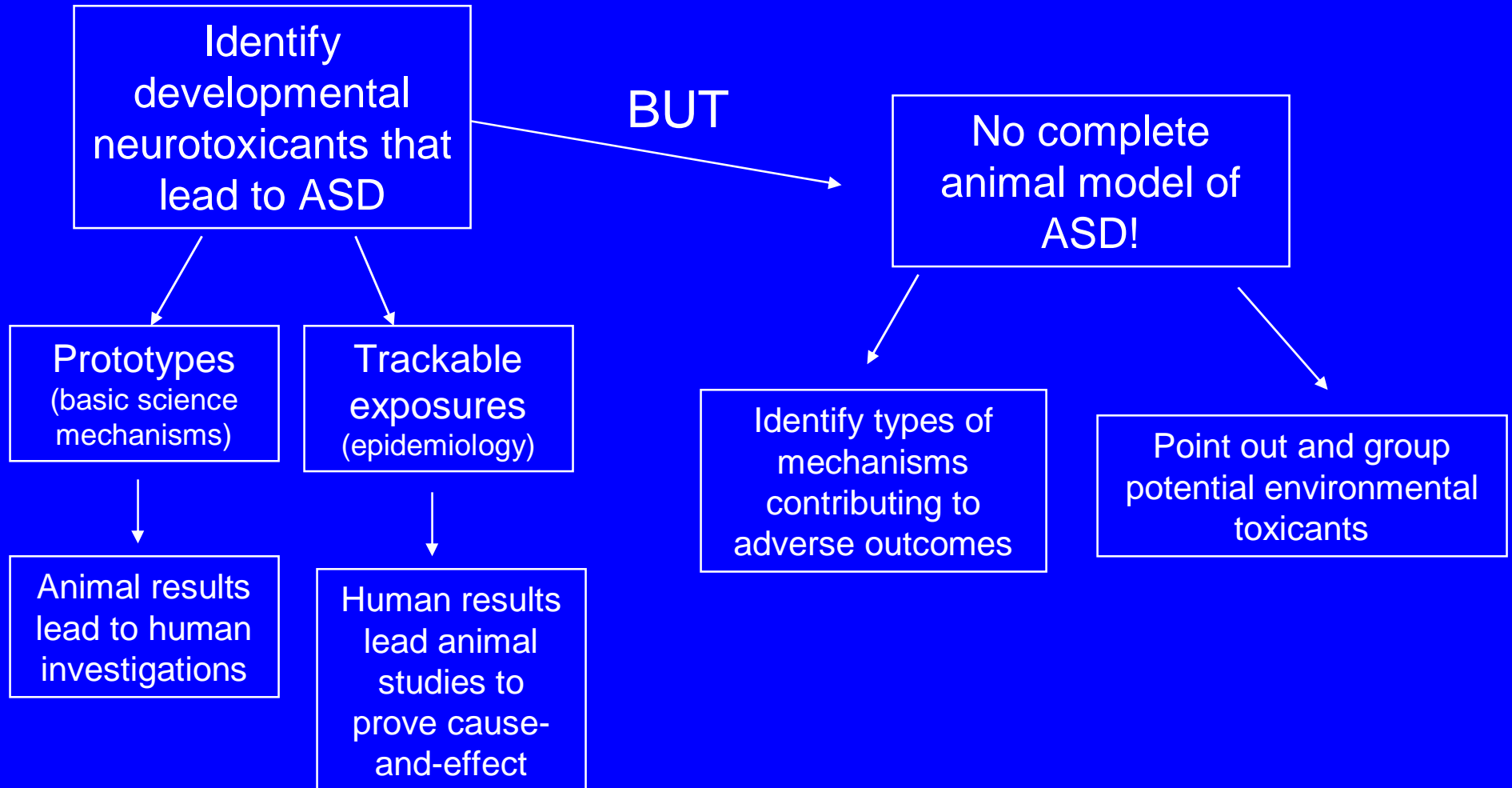


How Animal Models May Be Used to Examine Potential Environment-Based Mechanisms

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Support: NIH ES10356

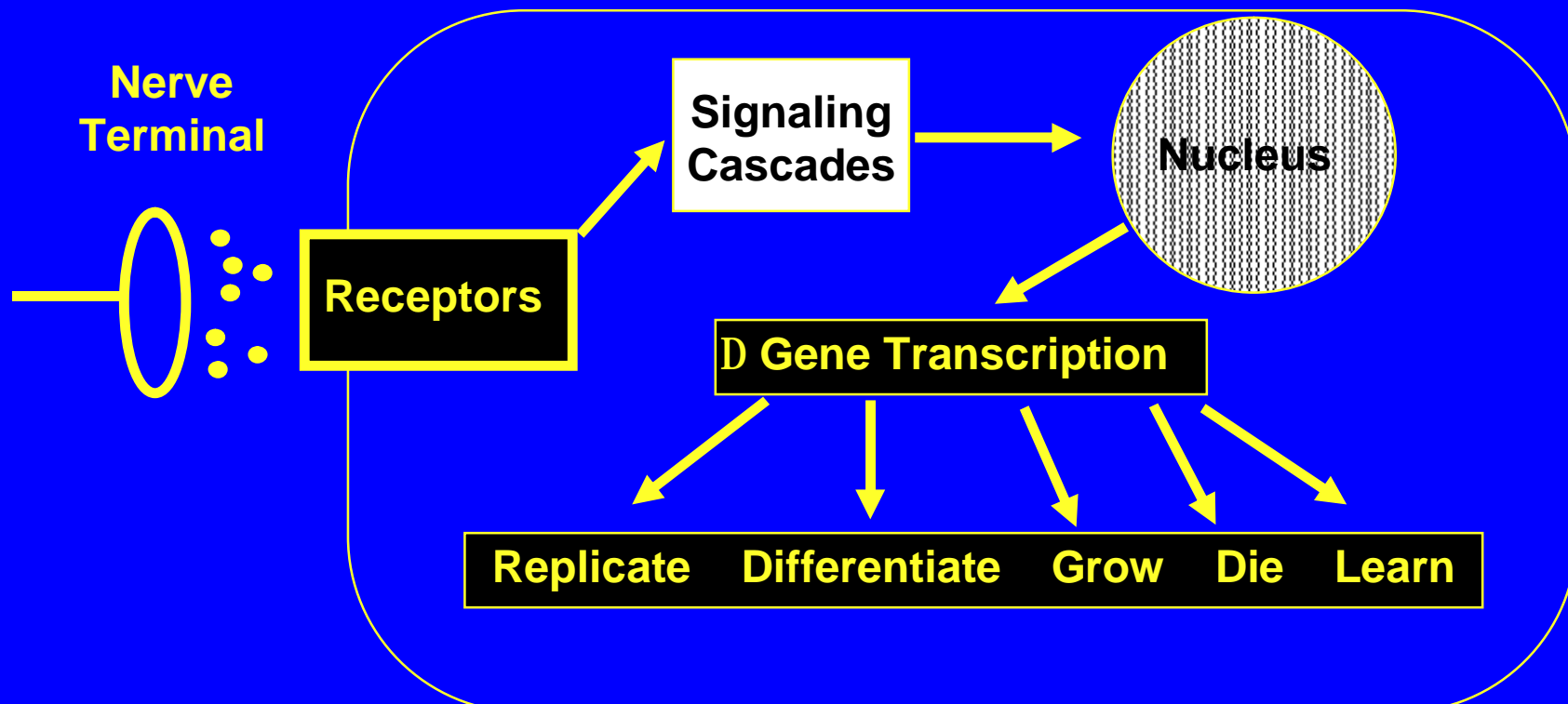
What are the Objectives of Animal Models?



Main Points

- Why do neuroactive agents produce permanent alterations with developmental exposures?
- Why is there a critical period for these effects?
- Why do apparently unrelated agents produce similar outcomes?
- Interaction of animal studies - human studies in ASD:
the example of terbutaline and beta-adrenergic receptors

Neurotransmitter Signals Control Cell Fate



The same neurotransmitter may be used for multiple decisions

Cells Learn During a Critical Period

Input During Critical Period



Change in Cell Differentiation



Permanent Change in the Response to Stimulation

Input After Critical Period



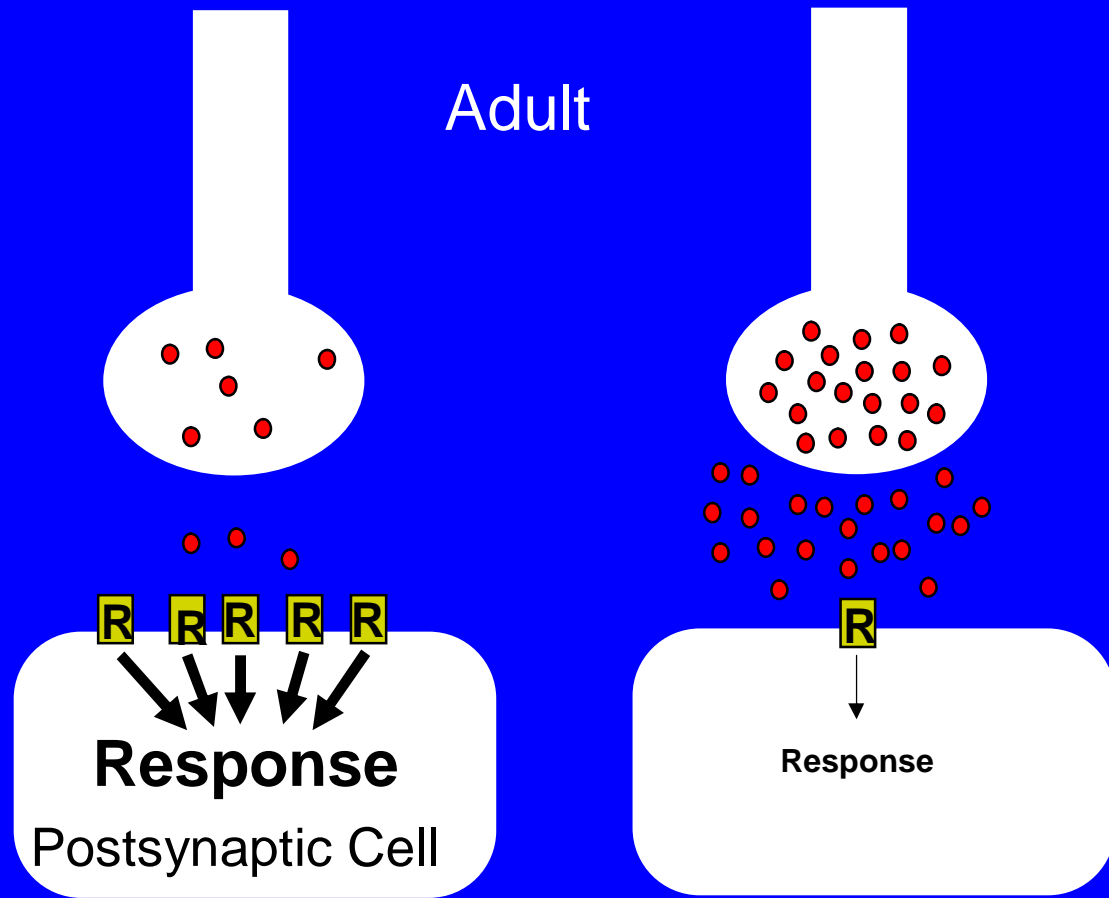
Short-Term Response Elicited



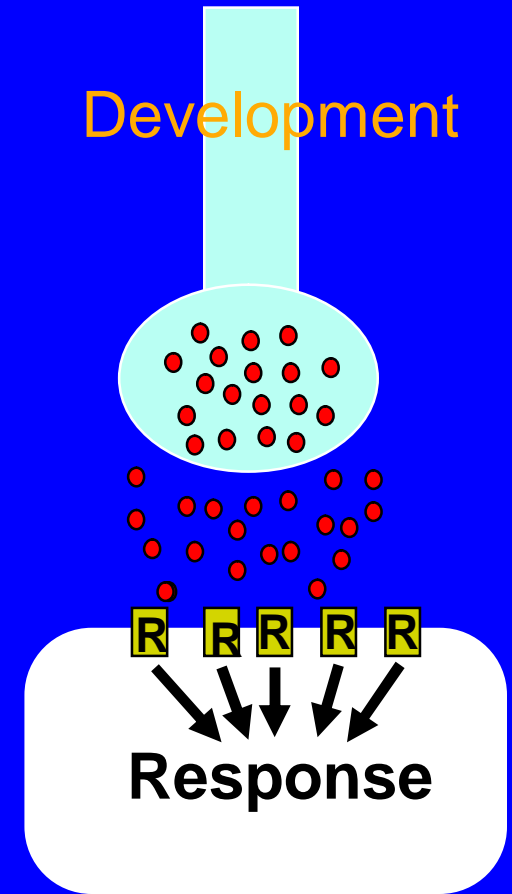
Short-Term, Reversible, Compensatory Adjustments

Postsynaptic Receptor and Response Regulation

Adult



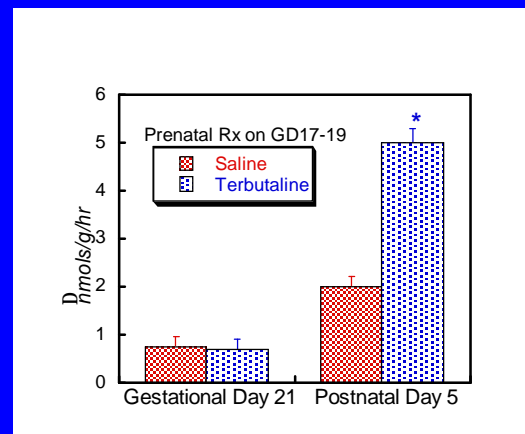
Development



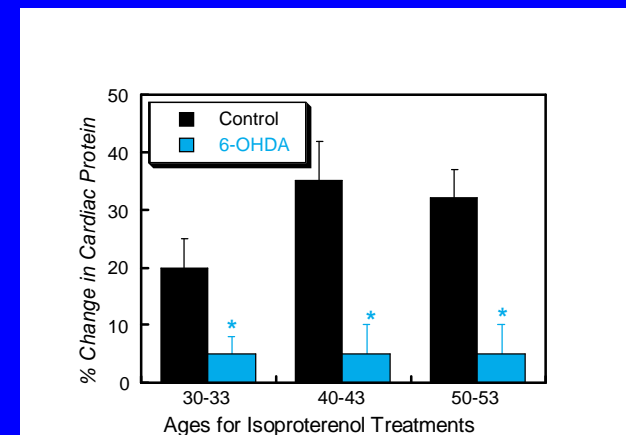
Positive Feedback for Receptor Control During Development - Peripheral Autonomic Function



Stimulation Reinforces the Response:
Lung Surfactant Synthesis



Early Interference Permanently
Blunts the Response:
Cardiac Hypertrophy Response



The same principles operate in the developing brain
The principles are universal
operate for other transmitters
operate in development of lower organisms

Neural Input Programs Response Development

- Critical period of stimulation
- Positive feedback reinforces response
- Changes differentiation fate of the cell
- Programming of future responses to stimuli
- Corollary: sending the “wrong” signal will produce miswiring
- Neuroactive drugs - drugs of abuse / therapeutic agents
- Environmental contaminants (organometals, insecticides)
- Stress / hormonal perturbations
- Terbutaline - an example relevant to ASD

Terbutaline (Mis)use in Preterm Labor

- Stimulates beta-adrenergic receptors - inhibit uterine contraction
- Crosses the placenta to stimulate fetal receptors
- Effective for 48 hr max but used widely for maintenance Rx
- Animal studies from our lab, 1980s-1990s
 - altered neural cell differentiation
 - receptor and signaling shifts
 - permanent changes in responsiveness
- Hadders-Algra 1986 - impaired school performance
- Pitzer 2001 - psychiatric, learning disorders

Terbutaline Is a Developmental Neurotoxicant: Effects on Neuroproteins and Morphology in Cerebellum, Hippocampus, and Somatosensory Cortex

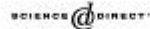
Melissa C. Rhoads, Frederic J. Seidler, Ali Abdal-Rahman, Charlotte A. Tate, Abraham Nyska, Heather L. Rincavage, and Theodore A. Slotkin

Neuroinflammation and Behavioral Abnormalities after Neonatal Terbutaline Treatment in Rats: Implications for Autism*

M.C. Zerrate, M. Pletnikov, S.L. Connors, D.L. Vargas, F.J. Seidler, A.W. Zimmerman, T.A. Slotkin, C.A. Pardo
JPET, in press



Available online at www.sciencedirect.com



Developmental Brain Research 157 (2005) 172–188

Research report

Critical periods for the role of oxidative stress in the developmental neurotoxicity of chlorpyrifos and terbutaline, alone or in combination

Theodore A. Slotkin^{*}, Colleen A. Oliver, Frederic J. Seidler

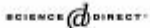
Departments of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC 27710, USA

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Developmental Brain Research 160 (2005) 209–230

Research Report

Imbalances emerge in cardiac autonomic cell signaling after neonatal exposure to terbutaline or chlorpyrifos, alone or in combination

Theodore A. Slotkin^{*}, Charlotte A. Tate, Mandy M. Cousins, Frederic J. Seidler

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Shares morphological, behavioral characteristics of autism
Excessive beta-receptor stimulation elicits oxidative stress
Evokes neuroinflammation
Critical period corresponding to 2nd trimester in human fetus
Decompensation of CVS function like that reported in autism

**β_2 -Adrenergic Receptor Activation
and Genetic Polymorphisms in Autism:
Data from Dizygotic Twins**

(J Child Neurol 2006;20:876-884)

Susan L. Connors, MD; Dorothy E. Crowell; Charles G. Eberhart, MD, PhD; Joshua Copeland;
Craig J. Newschaffer, PhD; Sarah J. Spence, MD, PhD; Andrew W. Zimmerman, MD

Continuous terbutaline exposure for 2 weeks or longer was associated with increased concordance for autism spectrum disorders in dizygotic twins (relative risk = 2.0), with a further increase in the risk for male twins with no other affected siblings (relative risk = 4.4).

A significant association was found between the presence of 16G and 27E polymorphisms in autistic patients compared with population controls ($P = .006$).

Prenatal overstimulation of the BAR by terbutaline or by increased signaling of genetic polymorphisms of the BAR that have diminished desensitization can affect cellular responses and developmental programs in the fetal brain, leading to autism.

CONCLUSIONS

- Animal models provide mechanisms for neurodevelopmental disorders
- Databasing - systematic exploration of the animal literature for developmental neurotoxicants and final common pathways suspected as factors for ASD
 - examples - terbutaline, organophosphates, agents producing oxidative stress
 - results from animals can be used to trigger studies of human populations for exposures and outcomes
- Added value from examining outcomes where exposures can be readily documented and that have specific mechanisms (eg terbutaline)

What tools from neurodevelopmental research will prove useful?

- In vitro models to better identify and characterize developmental neurotoxicants
 - siRNA to isolate specific mechanisms potentially involved in ASD
 - cells humanized with polymorphisms (receptors, other?) associated with ASD
 - microarray “fingerprints” for developmental neurotoxicity, focusing on ASD-related pathways (e.g. oxidative stress, neuroinflammation)
- Lower organism models: *C. elegans*, zebrafish, sea urchins
- Peripheral surrogates predicted by common outcomes for autonomic and CNS effects -diagnostic/mechanistic applications