

Environmental Chemicals and the Developing Brain

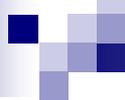
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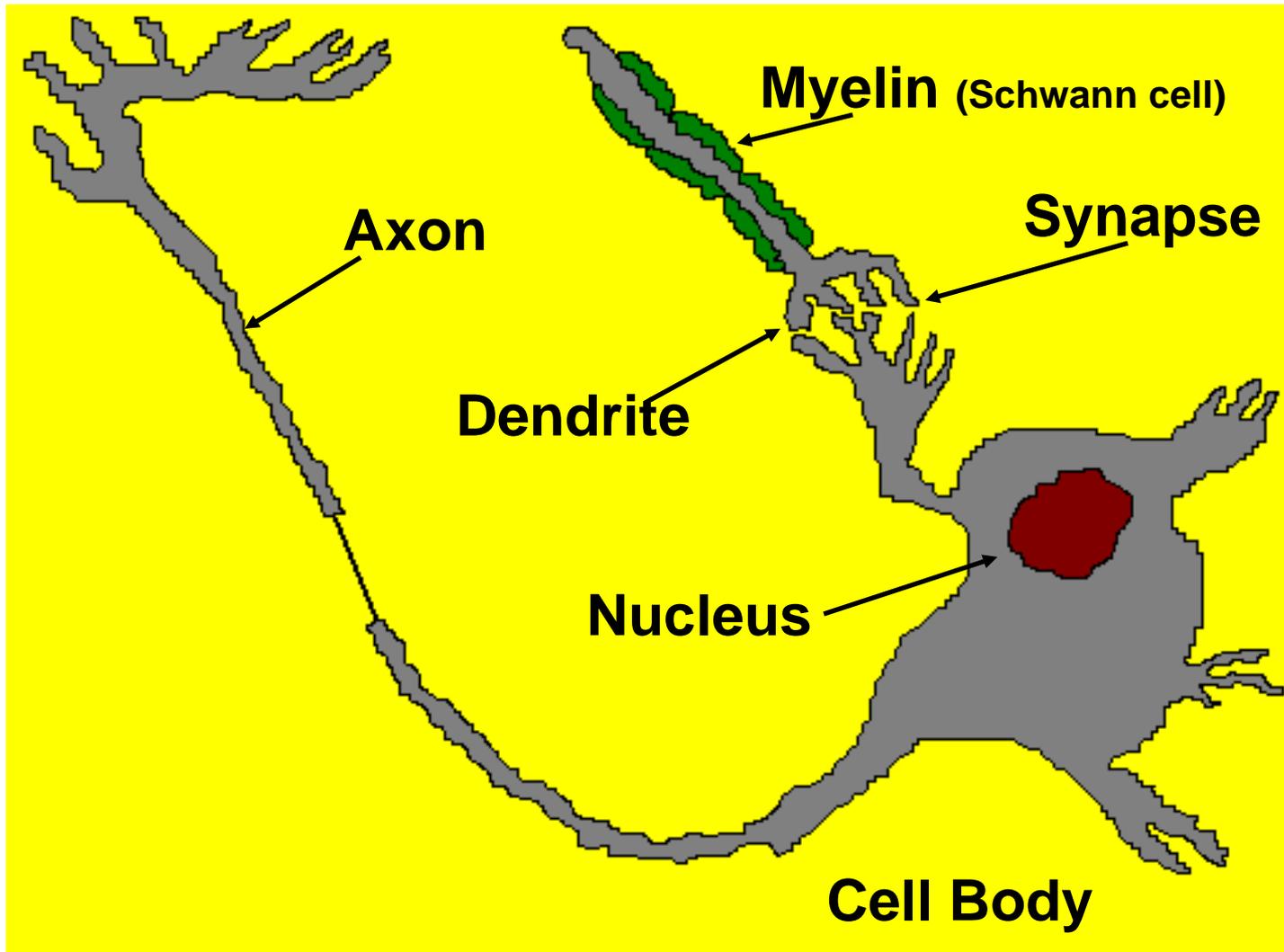
What in our environment causes neurotoxicity?

**Wide range of agents – chemical,
physical, psychological**

Chemical Developmental Neurotoxicants

- Metals
 - Lead, manganese, arsenic, mercury,
- Organic chemicals
 - PCBs, DDT,
 - Solvents
- Pesticides
 - Organophosphates, Carbamates
- Drugs
 - GHB, cocaine, benzodiazepine, ketamine

Neuronal Cells- the basic target





Neurotoxicology: Timing Matters

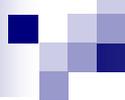
- Vulnerable periods
 - Childhood
 - Neurodevelopment
 - Elderly
 - Neurodegeneration

Types Of Neurotoxicity

- **Neurodegeneration**
 - **Neuronopathy**
 - Cell Death. Irreversible – cells not replaced.
 - MPTP
 - **Axonopathy**
 - Degeneration of axon. Reversible to a point
 - Hexane, Acrylamide
- ***Neurodevelopmental Toxicity***
 - **Myelinopathy**
 - Damage to myelin (impair electrical signals)
 - Lead, Hexachlorophene
 - **Transmission Toxicity**
 - Disruption of neurotransmission
 - Organophosphate pesticides, Cocaine, DDT, Lead
- ***Types of toxicity are not mutually exclusive***

Why are children more susceptible?

- Similar lists of toxic chemicals for children vs adults
- Lower dose per kg body weight impact children more relative to adults
- In the developing brain chemicals don't kill neurons
 - In adults with neurodegeneration - neurons die.

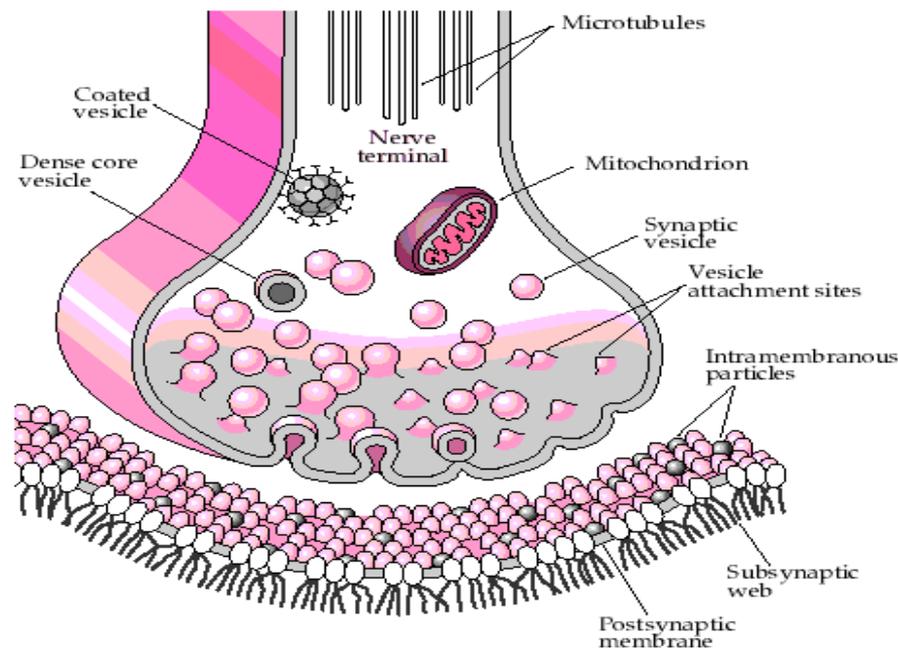


Biological Vulnerability- Neurodevelopment

- Construction of the central nervous system (CNS) begins in utero,
- Continues throughout childhood and involves the production of 100 billion nerve cells and 1 trillion glial cells.
- Cell migrate, differentiate, and form synapses

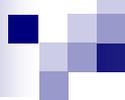
Synapses

- Transmit signals between neurons
 - Environmental stimuli will cause neurons to fire
 - Neuronal/synaptic firing is a signaling process to mold the synaptic architecture of the brain



How does the Brain Build this Network?

- Some of it is stochastic
 - Synapses are made by the billions, and in some respects randomly, between neurons.
 - We make a net gain in synapses from fetal life till about age 2 years
 - Then the number of synapses in our brain starts to decrease
 - Why?



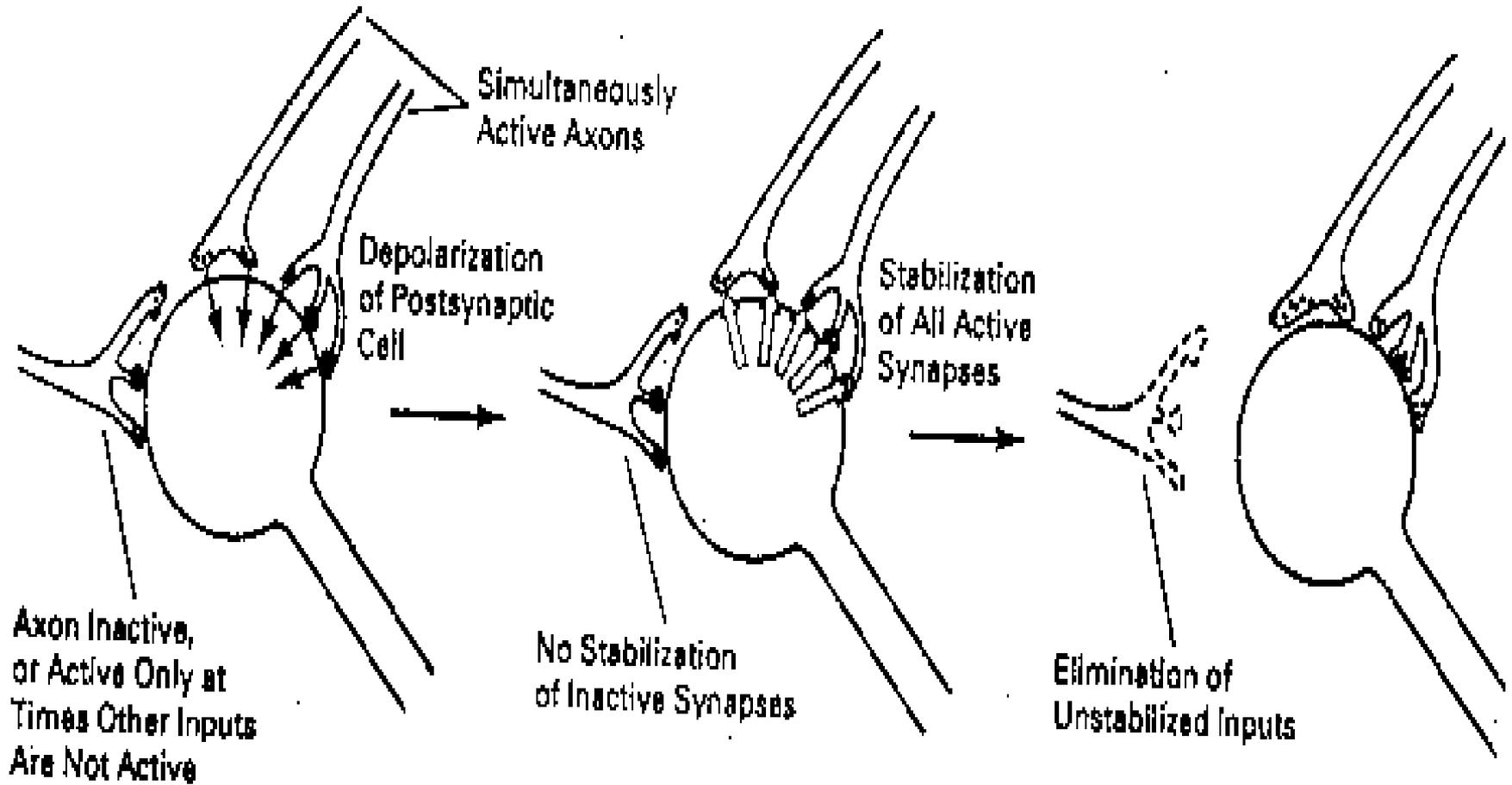
Synaptic Network

- Environmental Stimuli cause nerves to fire:
- When they fire, neurotransmitters are released into synaptic junctions
 - This releases growth factors
 - Signals that this is an important neuronal connection (i.e. it gets used)

Synaptic Pruning

- Environmental stimuli mold the CNS.
 - Synapses that produce function are repeatedly fired and kept
 - Synapses that are dormant are deleted
- In other words there is a “natural selection” process
 - Functional synapses release growth factors
 - Nonfunctional synapses do not release the growth factors

Hebb Synapses



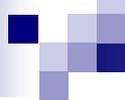
Weisel and Hubel

- Newborn kittens

- Patch one eye for one month
- Retinal development (specifically the development of neuronal connections) in the patched eye would not occur.

- Patch Adult cat eye for one month

- Compare neuronal networks between patched and unpatched eye
 - No difference than comparing unpatched cats



Implication

- Natural Selection is not just a process by which genetic variants are selected in Evolution
- Neuronal Cells and synaptic networks also undergo a process of natural selection

So how do Chemicals affect Development?

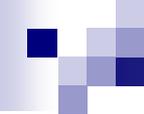
- Lead as a “paradigm” toxicant
- At “low” doses (blood lead around 5-10 ug/dL)
 - Lead will interact with Protein Kinase C
 - Stimulate neurotransmitter release
 - Neurons fire in the absence of an appropriate environmental stimuli
 - Lead mimics calcium
 - Calcium is critical to nerve signal transmission
 - Calcium enters neurons during depolarization
 - Lead blocks calcium channels

Lead generates “noise” instead of “signal”

- Net effect
 - Lead stimulates nerves to fire in a more stochastic (i.e. random), fashion
 - Lead also inhibits neurotransmission (both appropriate neurotransmission and inappropriate neurotransmission)
- Makes it hard to think/concentrate
- Changes the underlying synaptic architecture, making it less efficient

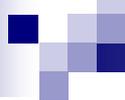
Childhood Lead Poisoning

- Lead exposure introduces noise to the process of synaptic pruning
 - Which synapses are chosen for survival and which regress becomes more random
- Net effect if prolonged- is that the underlying neuronal networks are less efficient.
- Structurally no damage is evident
- Functionally, deficits are measurable.



Plasticity

- The brain's capacity to diminish the effects of toxic insults
 - This occurs through the same processes as synaptic selection
 - In other words plasticity allows for new connections to be made which improve function following an insult
- Maladaptive vs adaptive plasticity

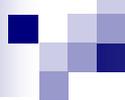


Stress and Social Environment

- **Another developmental toxicant**
- **Chronic Stress known to impair memory and learning capacity**

Non-chemical Toxicants- Psychological Stress

- Psychological stress - activates Hypothalamous-Pituitary-Adrenal (HPA) axis- increases cortisol
- Hippocampus - highest density of glucocorticoid (cortisol) receptors
 - modulate neuro and synaptogenesis
 - acutely, stress enhances memory formation,
 - chronic stress appears to inhibit it

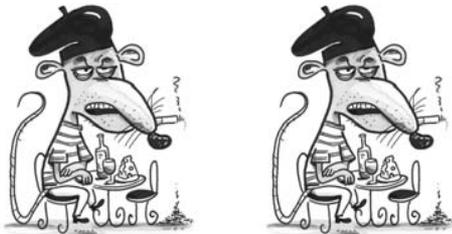


Why is this important?: Handling Paradigm and Memory/Learning

- Licking/grooming in mothers is stimulated by human handling of pups.
- Maternal LG and Arch back nursing behaviors program more appropriate long term HPA axis response to stress.
- Maternal LG/ABN clusters in family lines
 - Is it genetic or environmental?

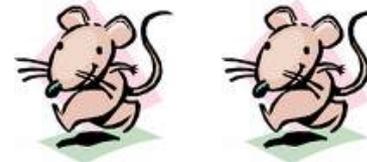
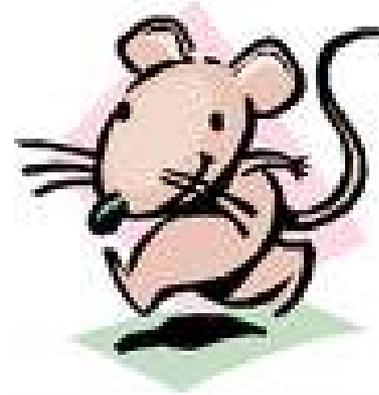
*Weaver et al. Epigenetic programming by maternal behavior
Nature Neuroscience |Volume 7| Number 8|August 2004*

low LG and ABN
mothers



Fearful offspring with brisk HPA stress response

high LG and ABN
mothers

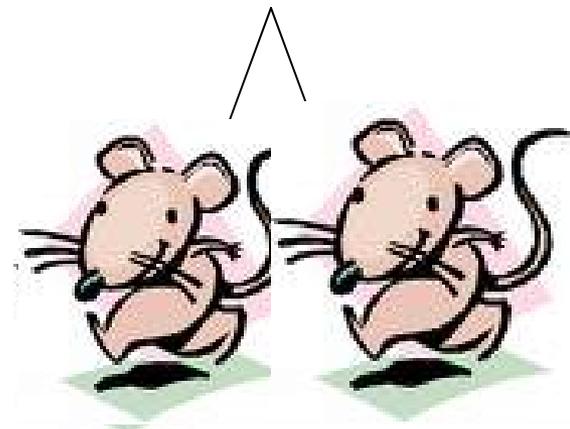
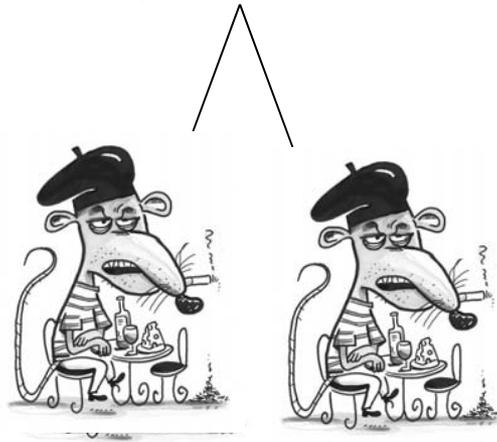
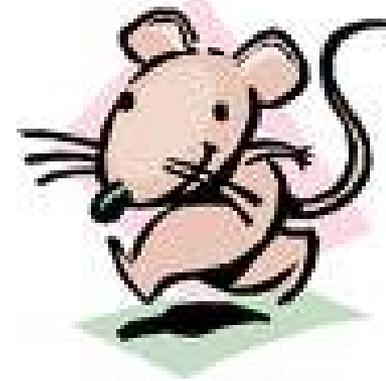


Less fearful offspring with more modest HPA stress response

EFFECTS OF CROSS-FOSTERING

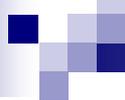
low LG and ABN mothers

high LG and ABN mothers



Fearful offspring with brisk HPA stress response

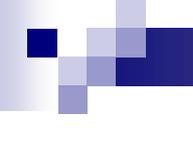
Less fearful offspring with more modest HPA stress response



Programming And Epigenetics

- Fetal origins of Disease

- Prenatal (and early life exposures), increase risk of late life disease
 - HTN,
 - Obesity
- Handling paradigm is an example of neuro-programming



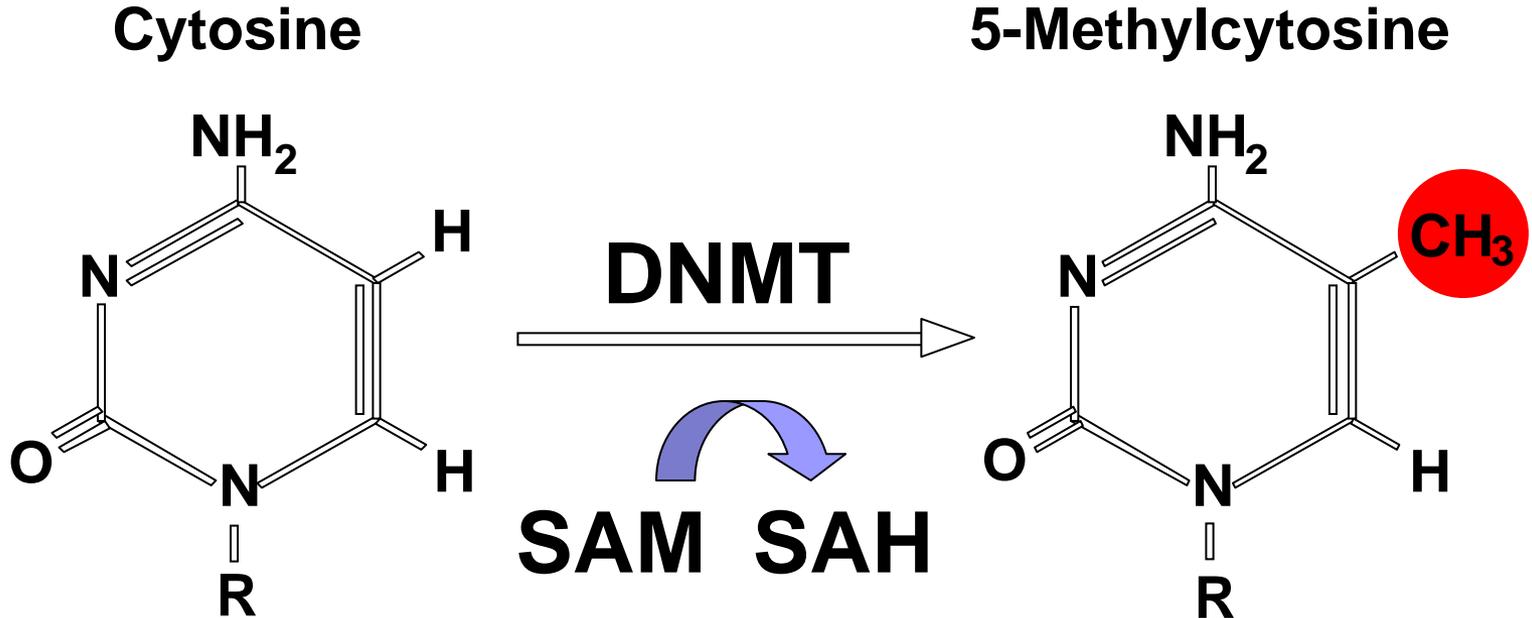
Epigenetics

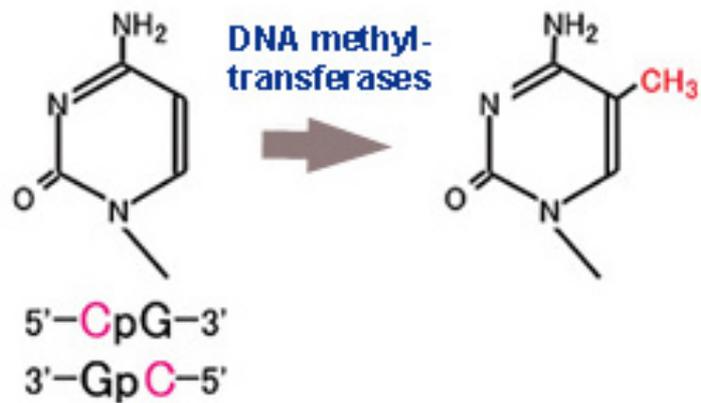
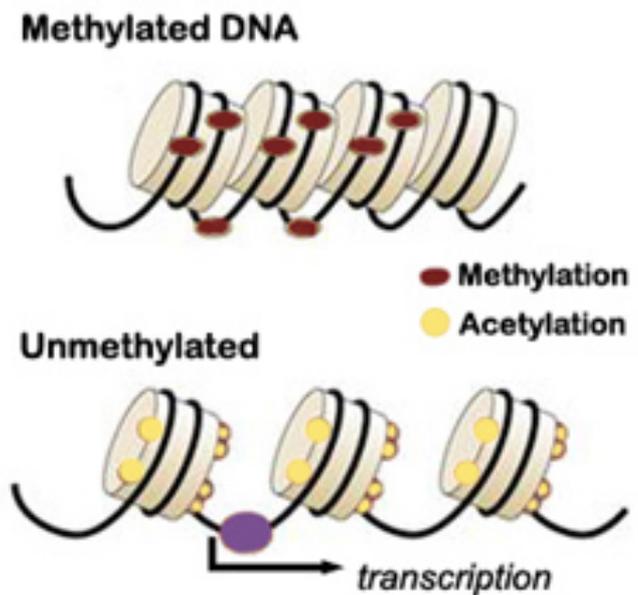
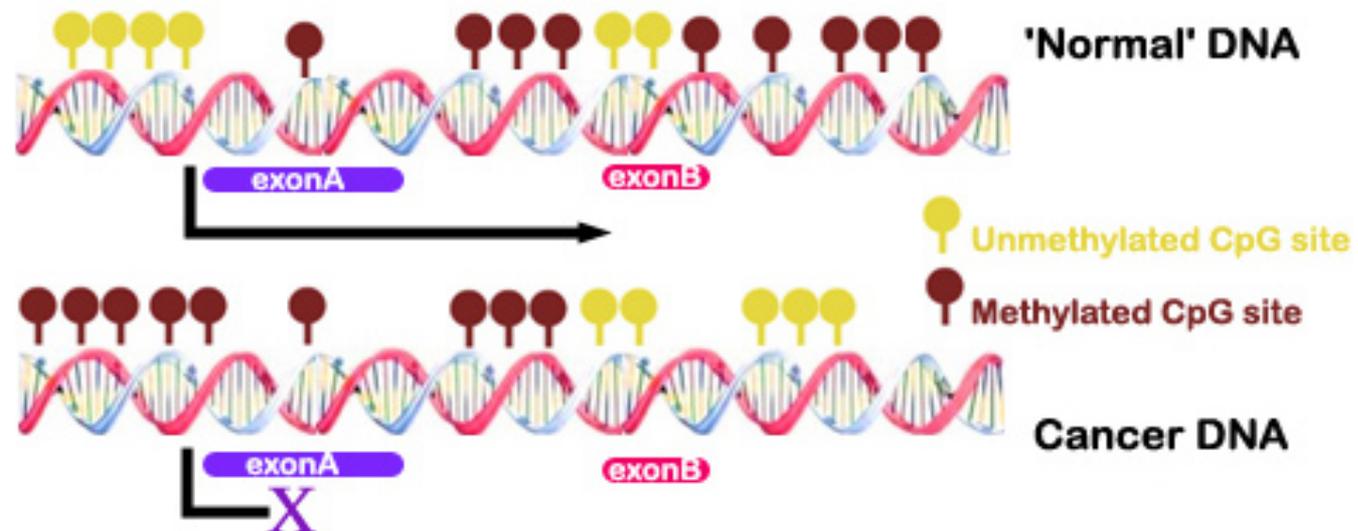
“The study of changes in gene function that occur without a change in DNA sequence”

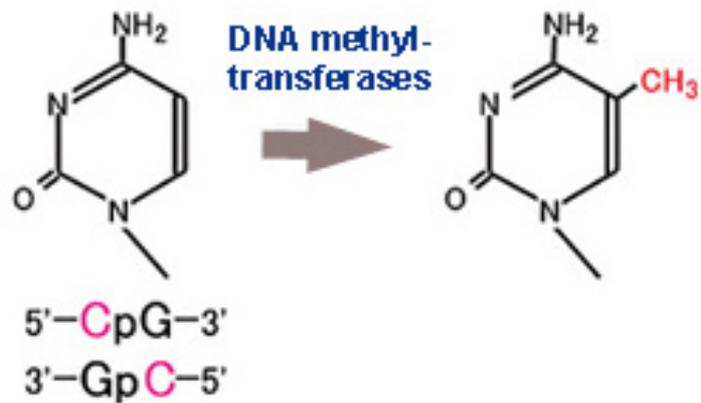
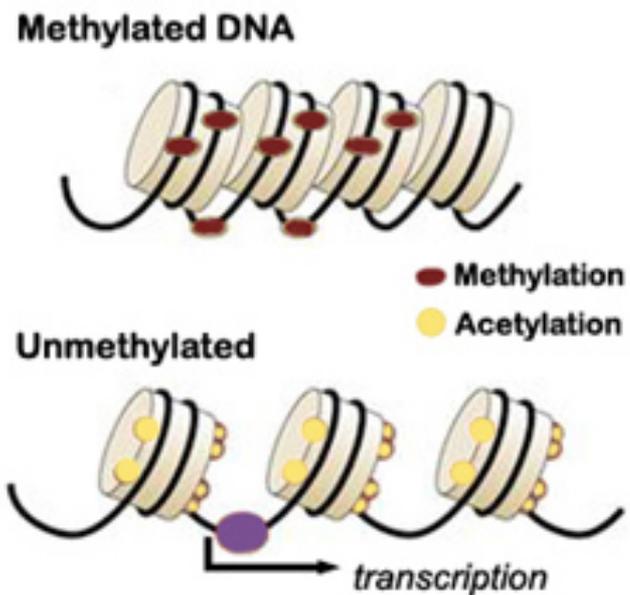
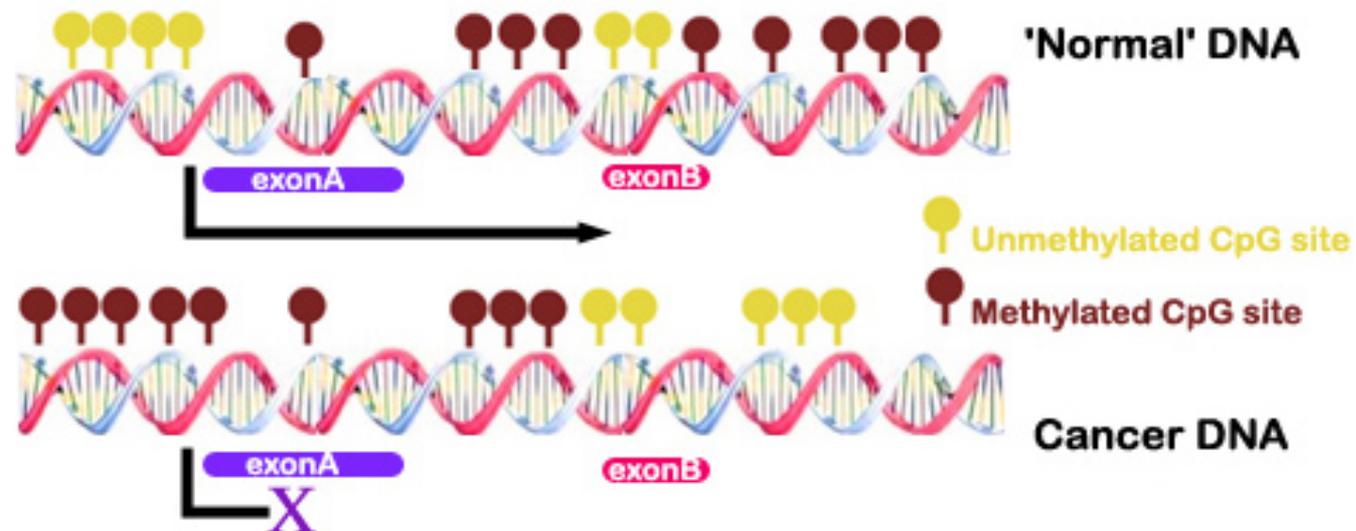
It is likely the most common method by which living organisms interact with the environment

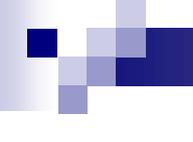
Has been shown to mediate Handling Paradigm

DNA methylation-An Epigenetic Mechanism



A**B****C**

A**B****C**



Epigenetics and the Brain

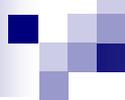
- Epigenetics plays an important role in synaptic pruning via environmental stimuli.
 - Epigenetic marks within neurons change with synaptic activity
- This "epigenetic opening" of synaptogenesis to environment is maximal during childhood
- Positive stimuli vs negative stimuli
 - Alters which synapses are pruned and which are kept

Handling Paradigm

- Weaver et al

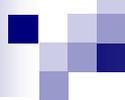
- Glucocorticoid receptor expression is inversely correlated with DNA methylation across Glucocorticoid Receptor in the brain

- **Matches the behavior of the mother and not the genetics of the offspring.**



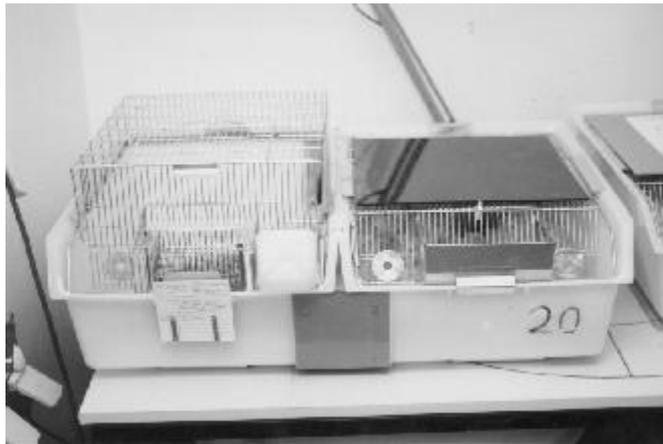
Toxicology and Social Environment

- How does this relate to toxicology?
 - Chemical exposures can have different effects depending on the context in which they occur.
 - Or their toxicity can be “treated” by changing the context in which an animal lives

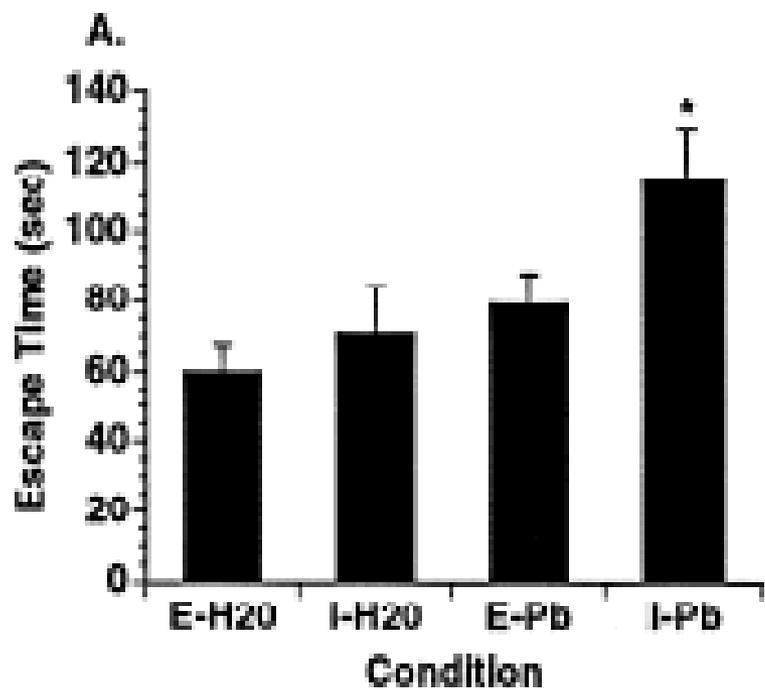


Social Environment and Lead Poisoning

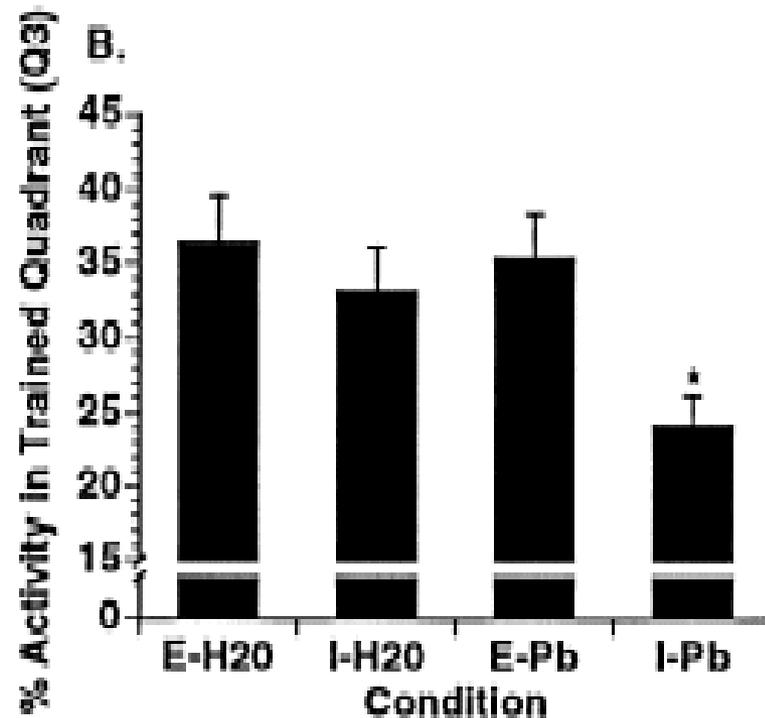
- Guilarte et al
- Lead poisoned animals during lactation
- Randomized to 2 groups
 - Animals raised in social isolation
 - Animals raised in groups with social stimulation
 - Tested on memory in Water maze

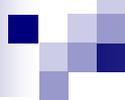


Acquisition Time



Probe Test



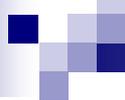


Lead and Social Interaction: Summary of how they relate

- The brain is “Plastic”
- Epigenetics mediates this “plasticity”
- The same properties that make children more susceptible to lead poisoning, make them susceptible to social stress
- Positive interventions may allow them to overcome toxic chemical insults

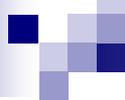
Treatment of Lead poisoned children

- At present there is none.
- Dogma is that once a child is lead poisoned- “The Damage is done”
 - Lead effects are indeed long lasting
 - But Cells don't die in childhood lead poisoning
 - And we don't really intervene when a child is lead poisoned.



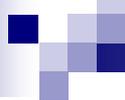
Treatment of Lead Poisoning

- Mechanisms of lead poisoning, coupled with the biology of developmental plasticity suggest treatment is possible
- Principle of Critical Developmental Windows suggests that timing is key.
 - Treat before the “epigenetic opening” closes



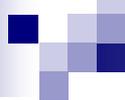
Interventions?

- Are there treatments that will improve cognition?
- Candidates include
 - Family therapy
 - Cognitive interventions
 - Social interventions
- Mix of above.



Cognitive Intervention

- Can we create a video game
 - That's fun
 - That teaches strategy
 - That exercises the brain with respect to working memory
 - That treats lead poisoning

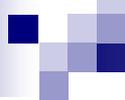


Summary

- Brain development requires the formation of efficient neuronal/synaptic networks.
- Environmental stimuli are signals which allow for “selection” of synapses.

Summary

- Lead at low levels
 - Stimulates neurotransmitter release
 - Stimulates neuronal firing
 - Blocks calcium channels which transmit electrical signals down neurons
 - Inhibits neurotransmission
- Net effect is to add noise to the Signaling process.
- Neuronal networks are less efficient
- No anatomical changes are seen.



Summary

- Social Context may modify rather than confound lead poisoning
 - Are social/behavioral/cognitive interventions a potential treatment for lead toxicity?

A forgotten field in Environmental Health

Question and Answer

**** Please remember to write your question on the index card found with your event materials and give them to the staff member collecting cards ****

Concluding Remarks

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