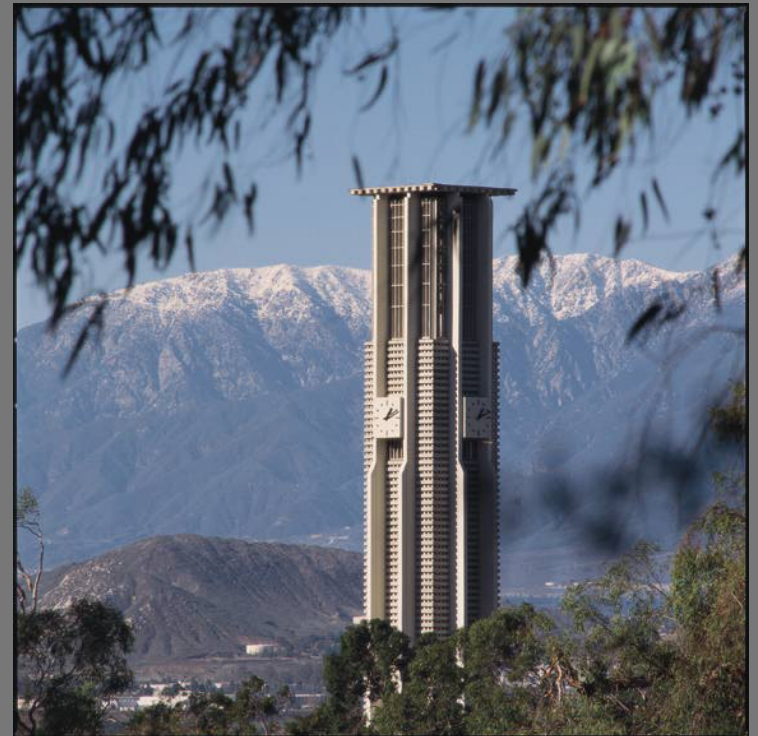


**Exposure to fire retardant chemicals before birth
can permanently harm the neuroendocrine
system, body water regulation, and
cardiovascular function**

M.C. Currás-Collazo

Dept. of Cell Biology & Neuroscience
University of California, Riverside



Presentation Outline

Part 1. Vasopressinergic Neuroendocrine System

Part 2. Neuroendocrine Effects of PCBs and PBDEs

Part 3. Effects of Perinatal PBDE exposure

Magnocellular neuroendocrine cell system

2 locations:

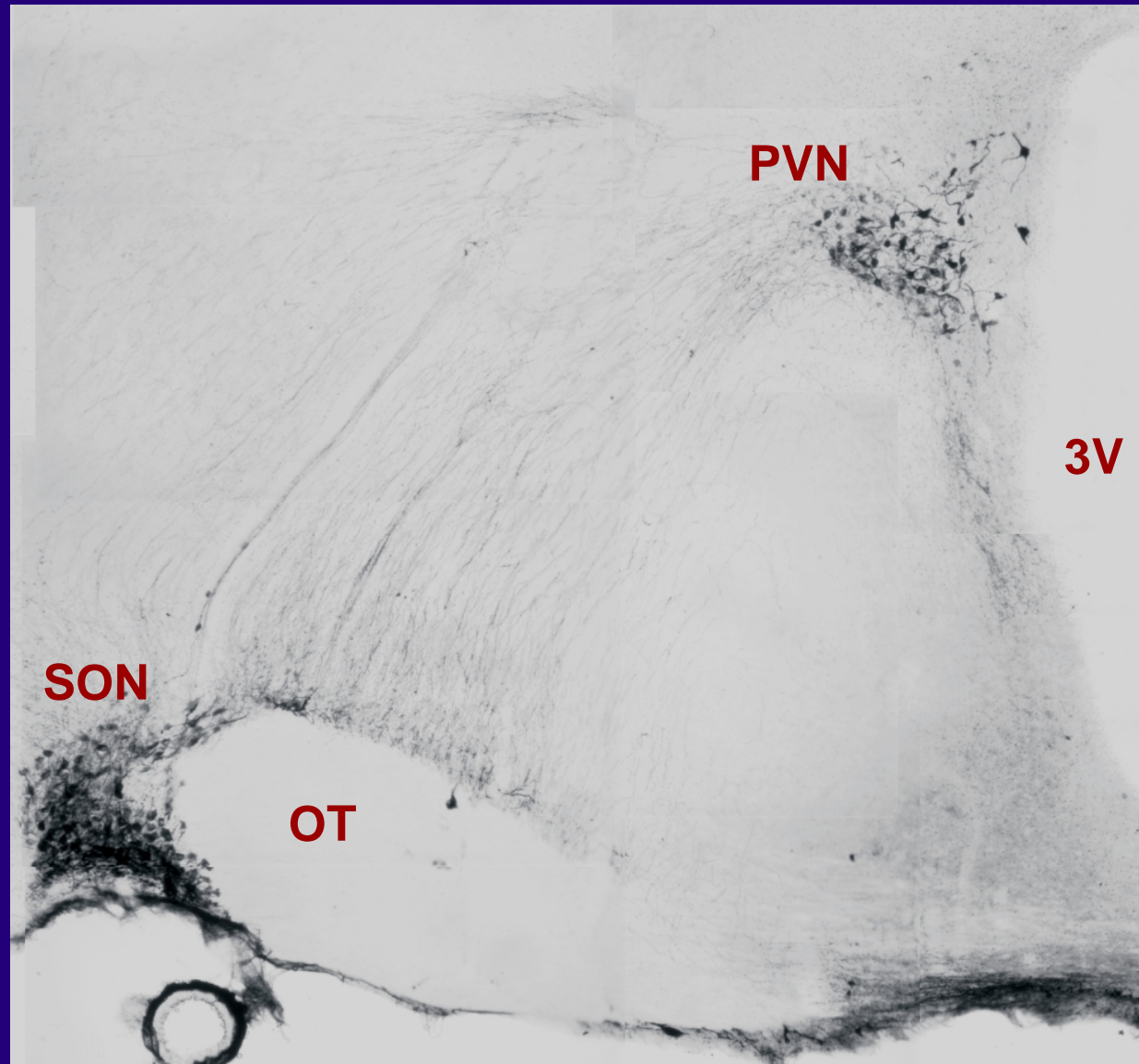
SON

PVN

2 populations:

Oxytocin

Vasopressin (VP)



VP-NP antibody gift from Dr. Gloria Hoffman, University of Maryland, Baltimore, MD

Hypothalamo-neurohypophysial system (HNS)

Stimuli:

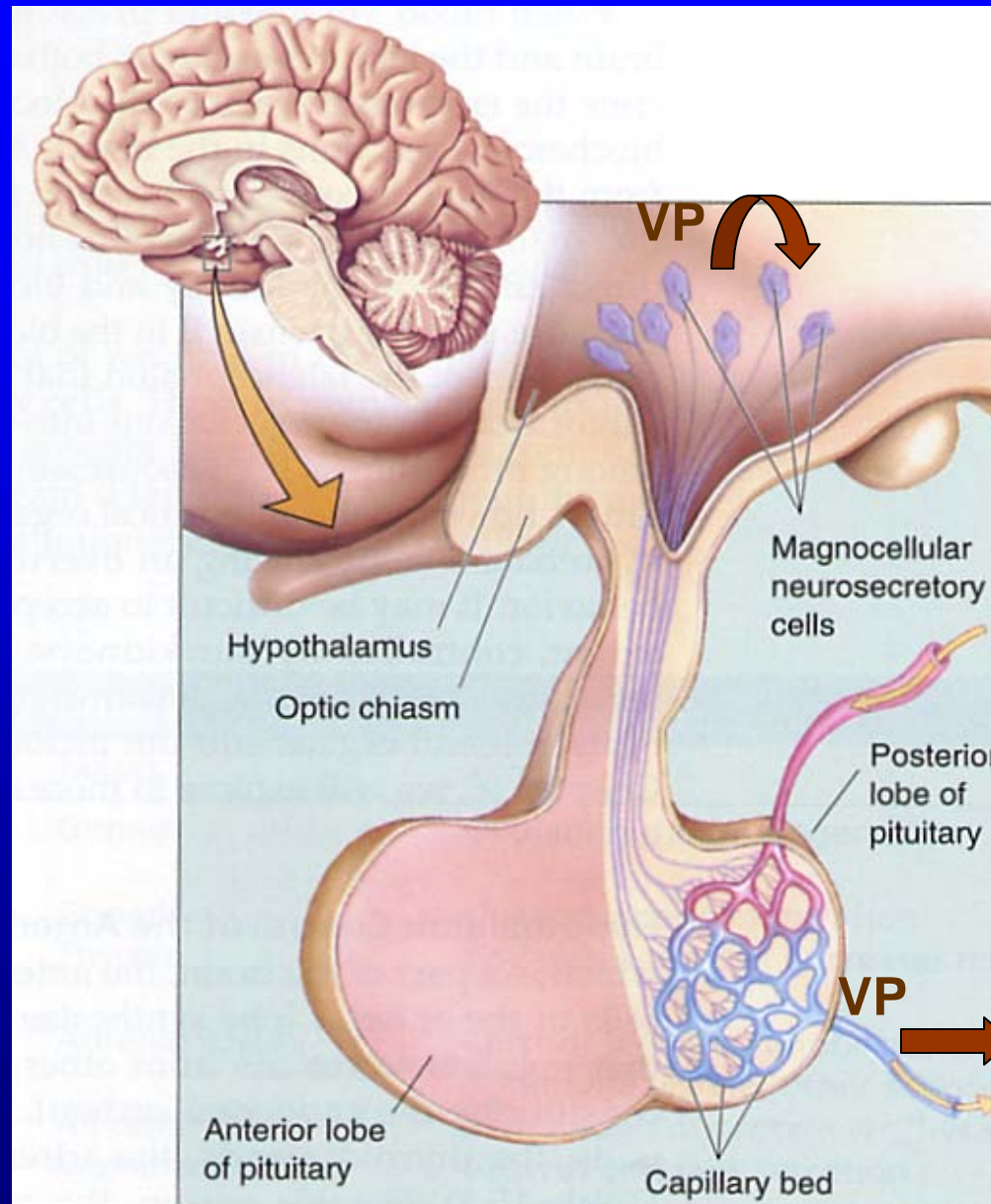
Hyperosmolality
Hypovolemia

Detectors:

Osmoreceptors
Baroreceptors

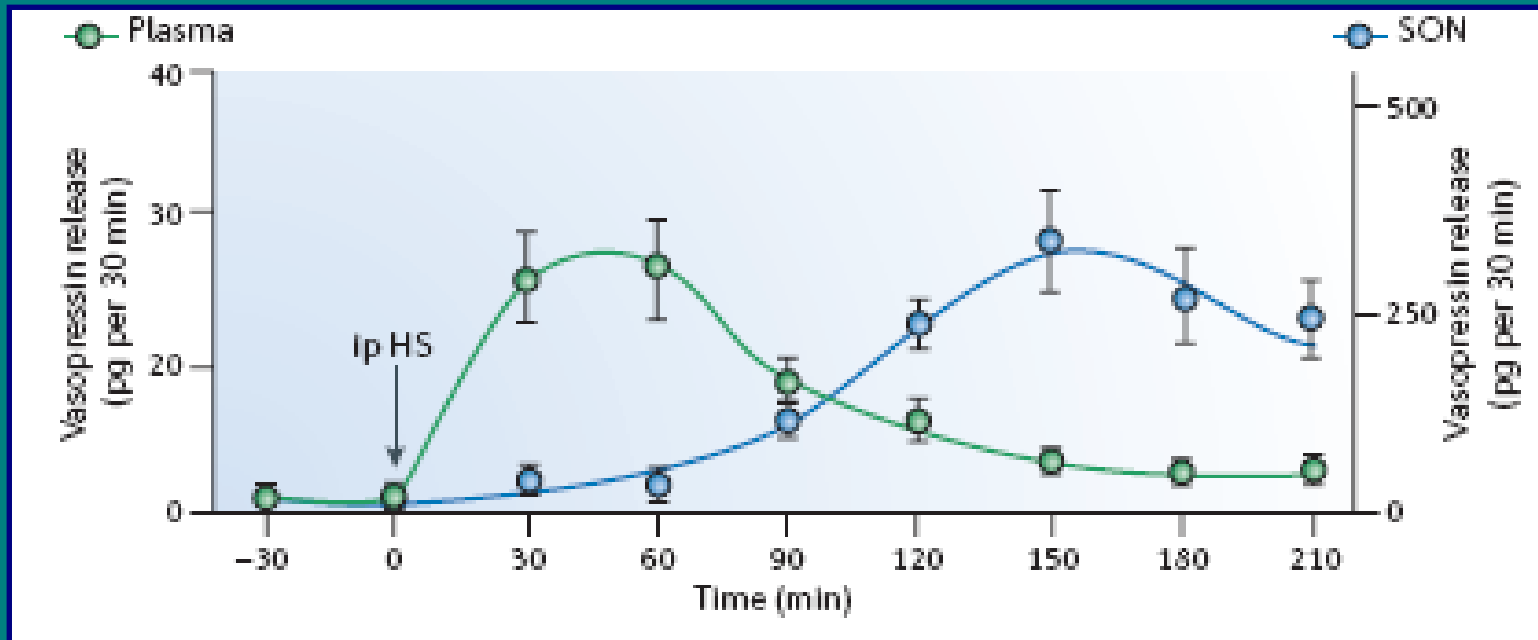
Effectors:

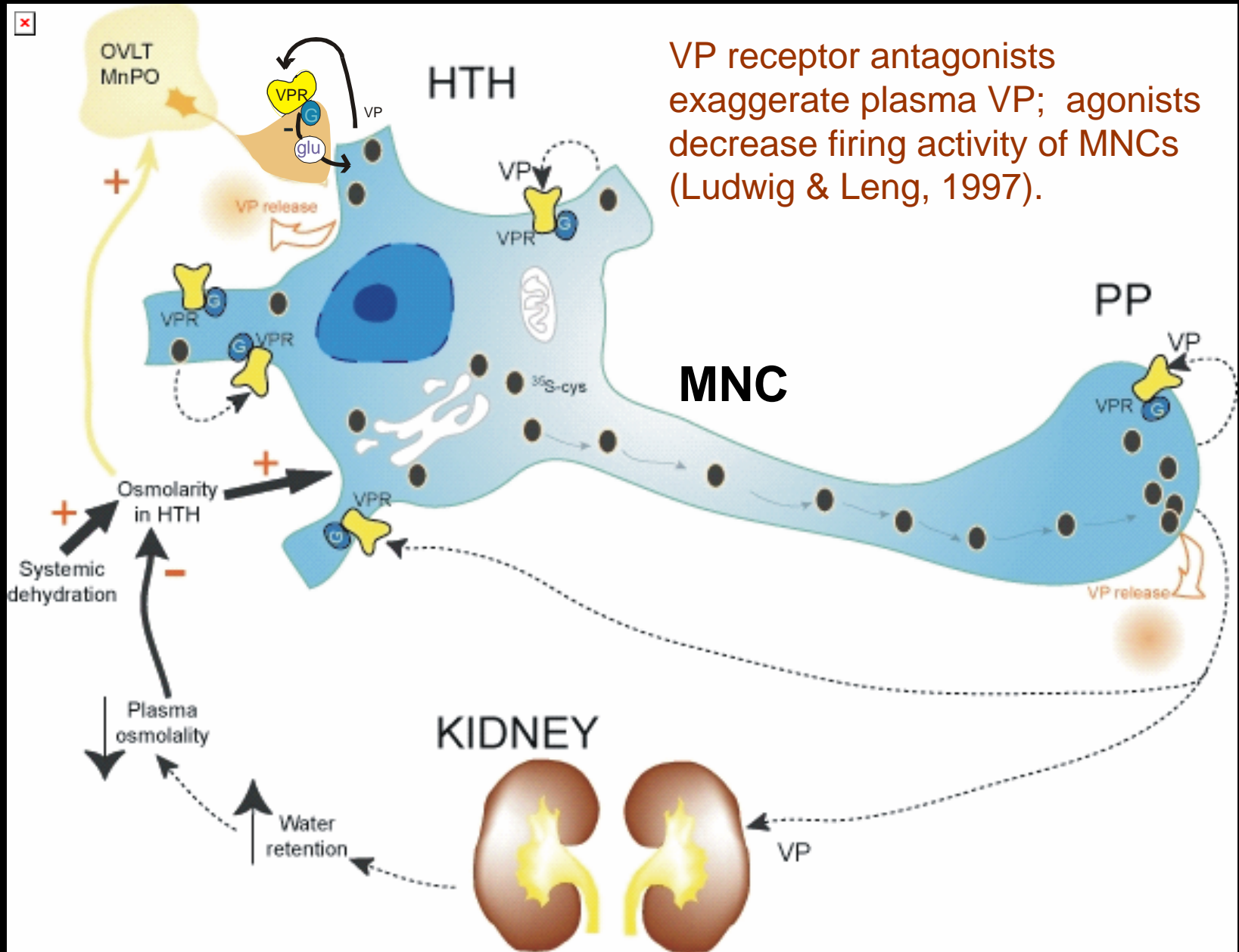
Magnocellular
neuroendocrine cells
(MNCs)



**Correctional
Mechanism:
Water retention
(kidney)**

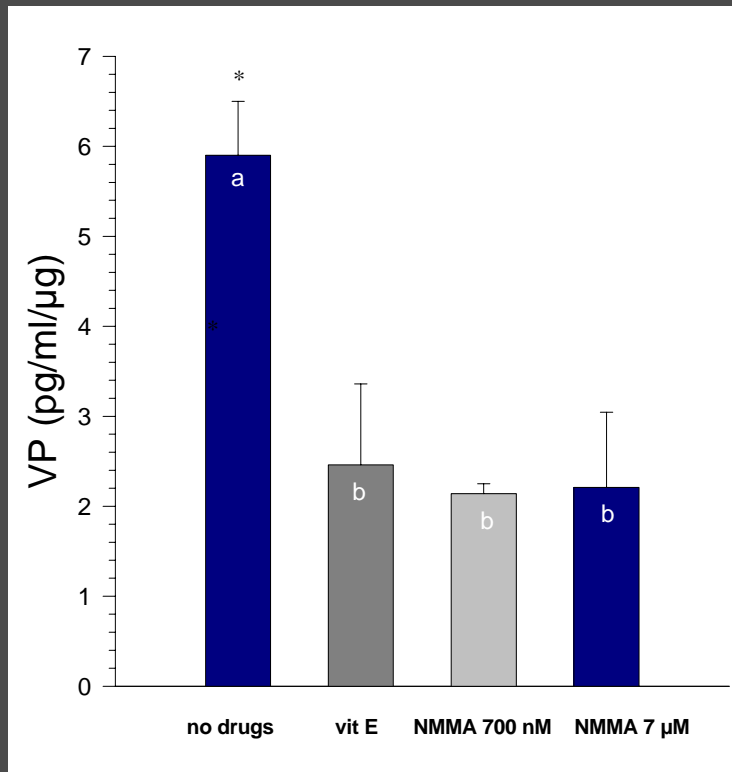
Coordinated but temporally segregated release



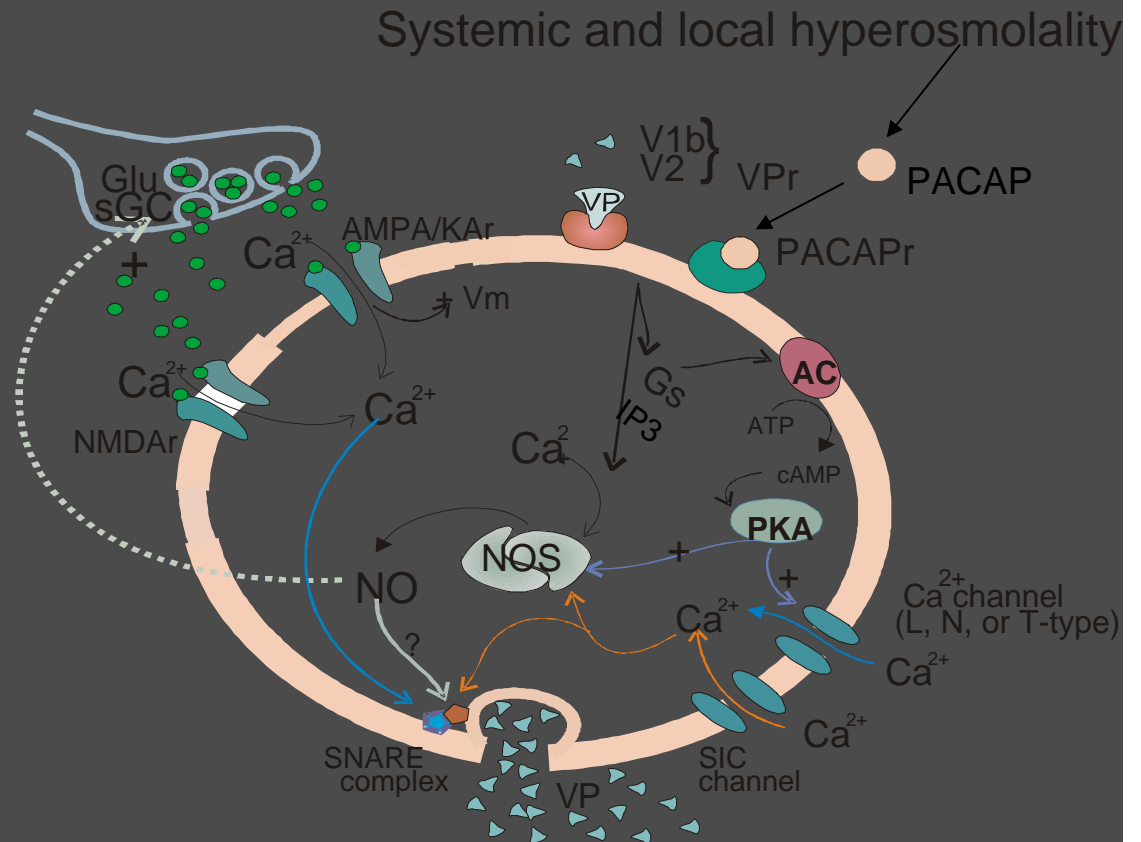


VP receptor antagonists exaggerate plasma VP; agonists decrease firing activity of MNCs (Ludwig & Leng, 1997).

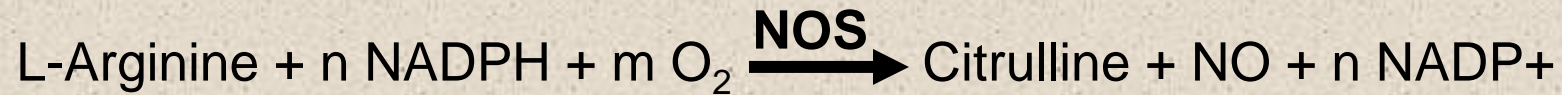
Central & Peripheral Vasopressin Release are Governed by Local Nitric Oxide



NO is a positive modulator of central VP secretion; negative modulator of VP hormone.



Osmotic activation of NADPH-diaphorase is deranged in aged rats

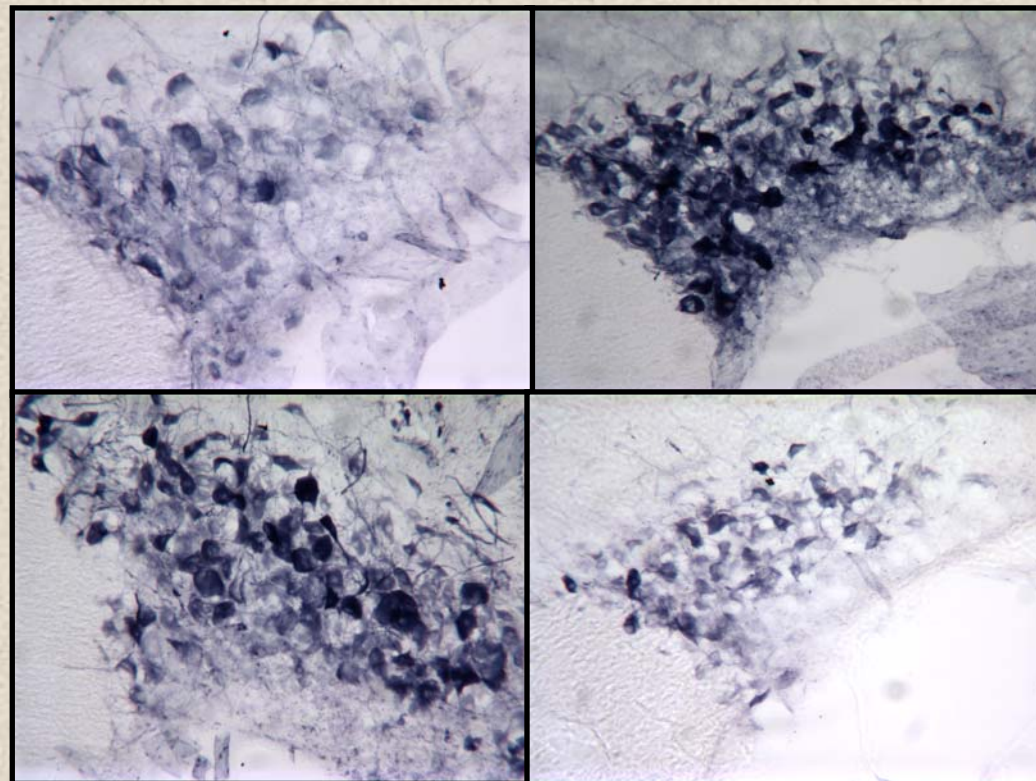


electrons transferred to nitro blue tetrazolium to produce a blue/purple color

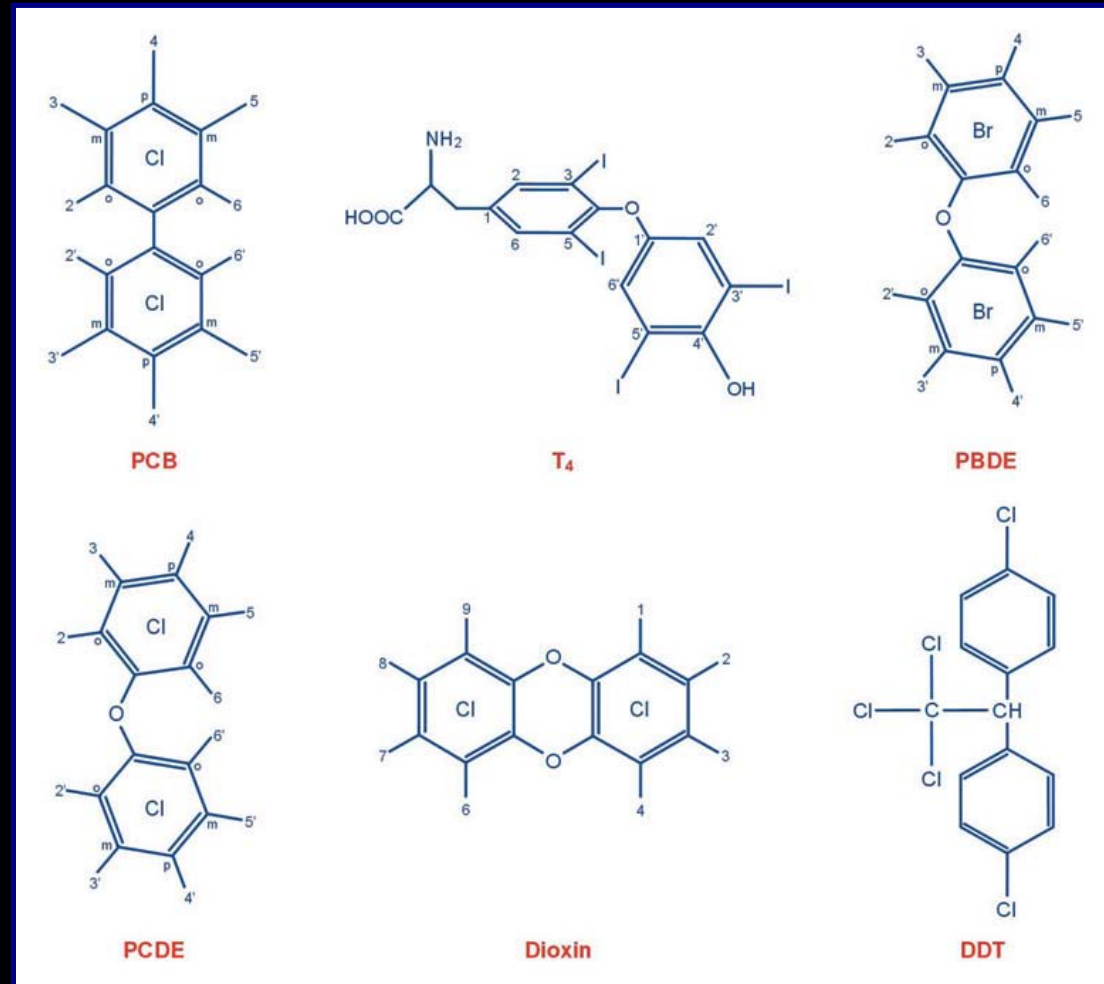
Normosmotic

Hyperosmotic

Control

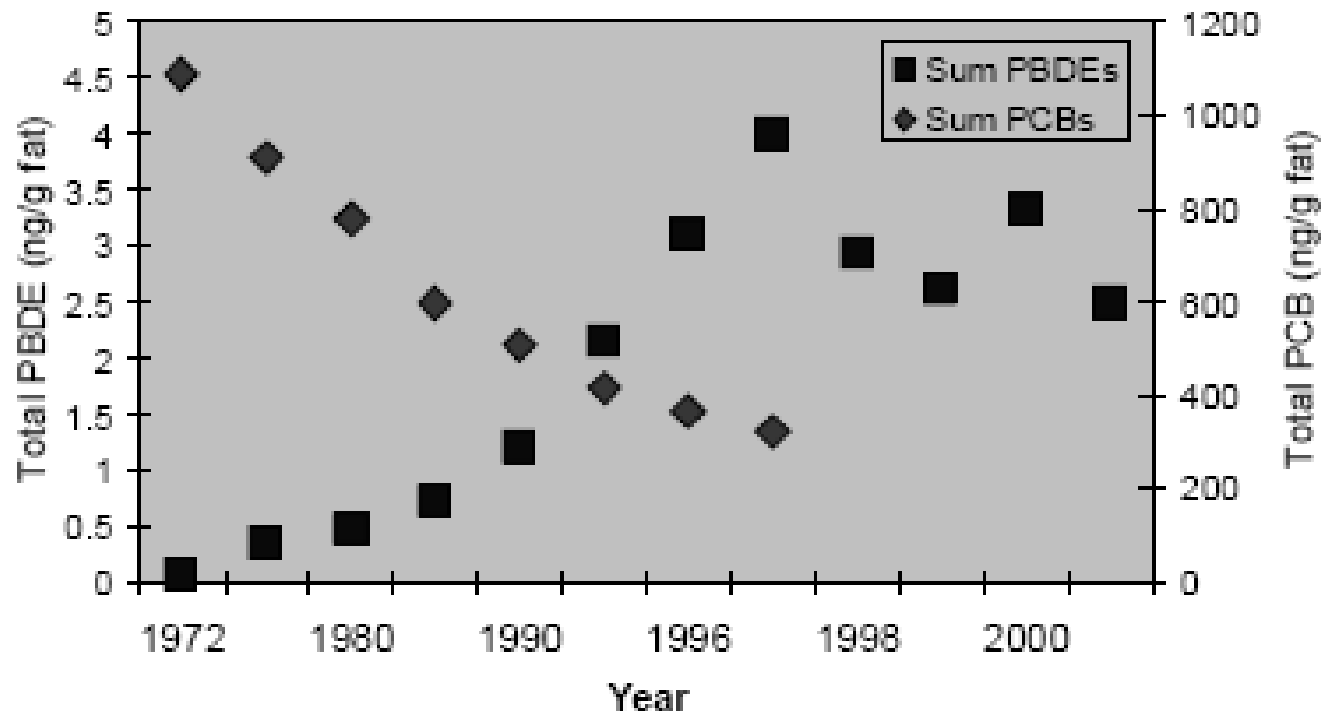


Several Persistent Organic Pollutants (POPs) Share a Similar Halogenated Biphenyl Structure



Kodavanti, PRS (2005) Dose-Response 3: 273-305.

Total PBDEs and Total PCBs in Human Milk in Sweden



PCBs in Our Environment

Chemically stable, high resistance to heat, low flammability and high dielectric constant; used in electrical equipment, heat transfer and hydraulic systems, plasticizers and lubricants

❖ High volume domestic production from 1929 to 1977. No longer being produced.

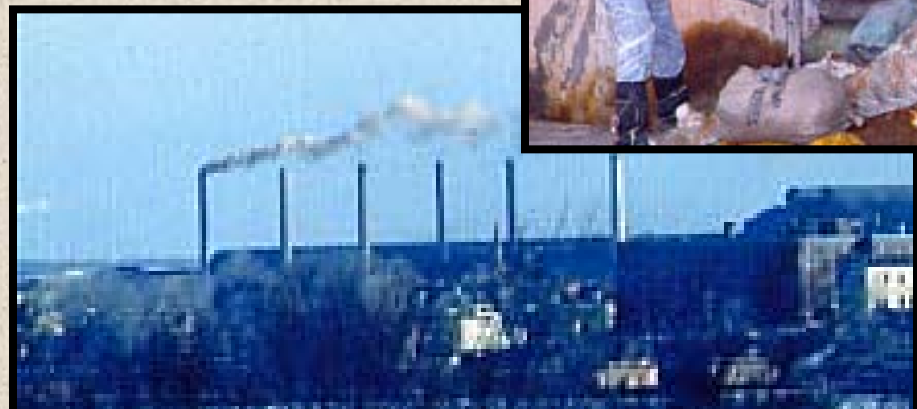


❖ PCBs persist in environment and biota: found in air, water, soil, and various foods.

❖ Sources: municipal waste disposal (landfills, sewage sludge), aquatic sediments, spills/leaks from PCB-tainted equipment and improper or illegal disposal (Safe, 1993).



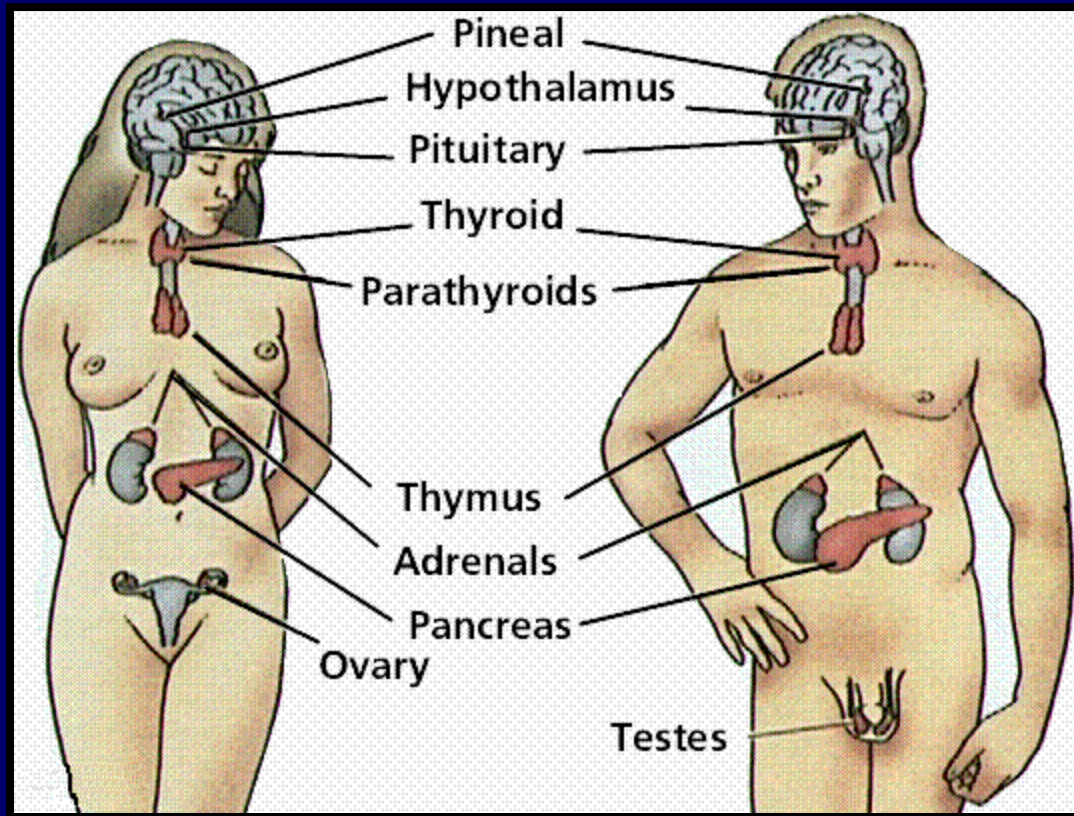
GE plant, Upper Hudson River, 1.3 M lbs discharged 1940s-1976



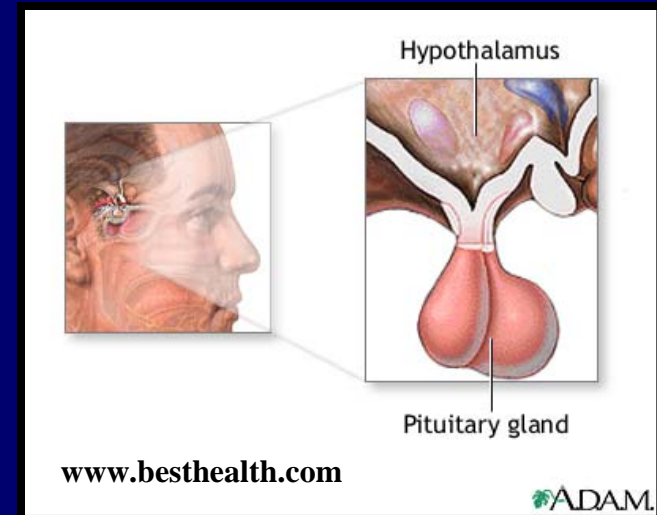
Presentation Outline

Part 2. Neuroendocrine Effects of PCBs and PBDEs

PCBs and PBDEs As Endocrine Disruptors



www.cartage.org.i



www.besthealth.com

ADAM.

Endocrine Disruptor: An exogenous substance which causes changes in endocrine function leading to adverse effects in an animal or offspring.

Some Adverse Health Effects of PCBs

Endocrine Disruption:

- altered thyroid hormone levels
- reproductive dysfunction

Syndrome-like variety of maladies

- Immunosuppression
- Respiratory Problems
- Hepatic and stomach damage
- Cancer: liver, lung

Diverse Neurological Effects

- disruption of learning, memory and cognition
(Jacobson & Jacobson 1996, Schantz and Widholm, 2001)
- decreased nerve conductance & numbness
- speech problems

Kodavanti, PRS (2005) Dose-Response, 3: 273-305

Carpenter, DO (2006) Rev Environ Health, 21(1): 1-23.

Experimental Design

Adult male Rats
Oral Dosing via Cheeto™ treats
Aroclor 1254; 30mg/kg/d X 15d



Osmotic challenge (day 15)

0.9% saline, ip
normosmotic

3.5 M NaCl (6
ml/kg) ip
dehydrated

VP levels in
plasma

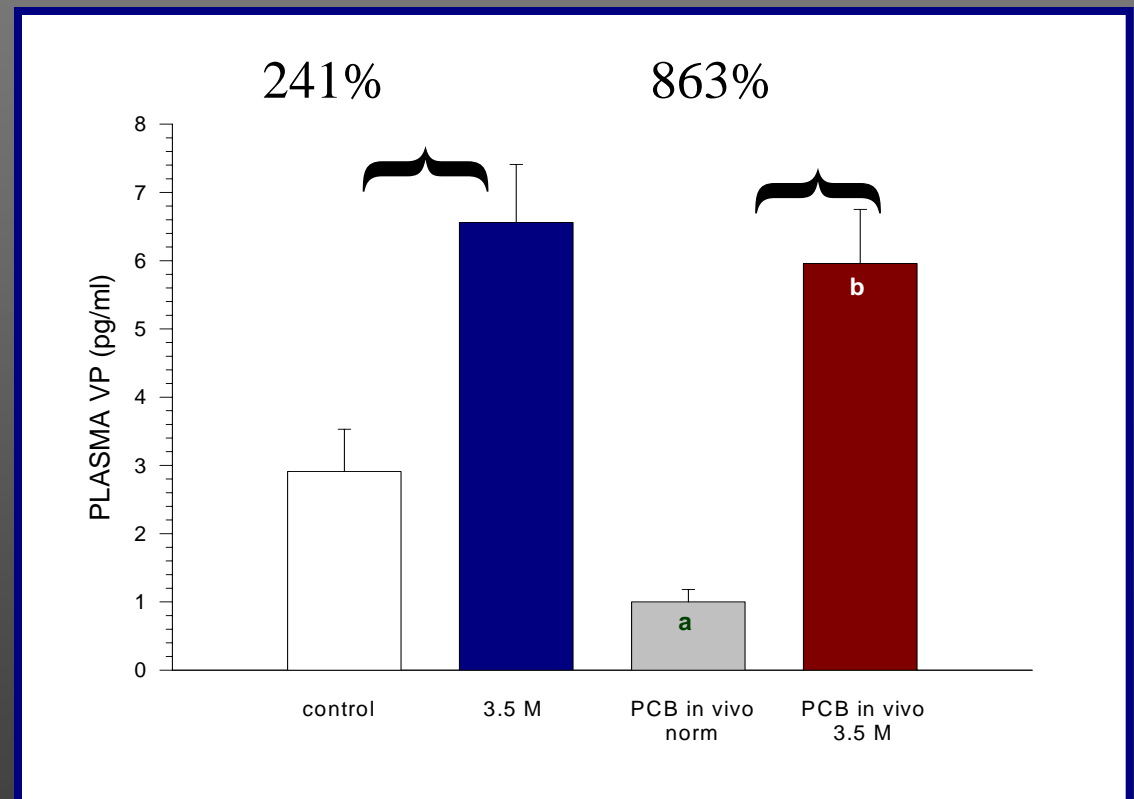
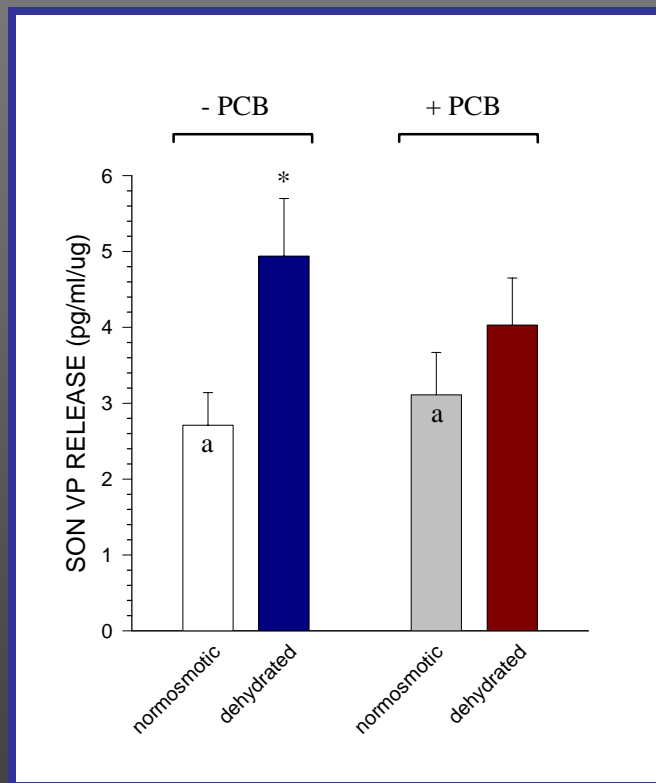
3-5 hrs *in vivo*

Measure plasma osmolality

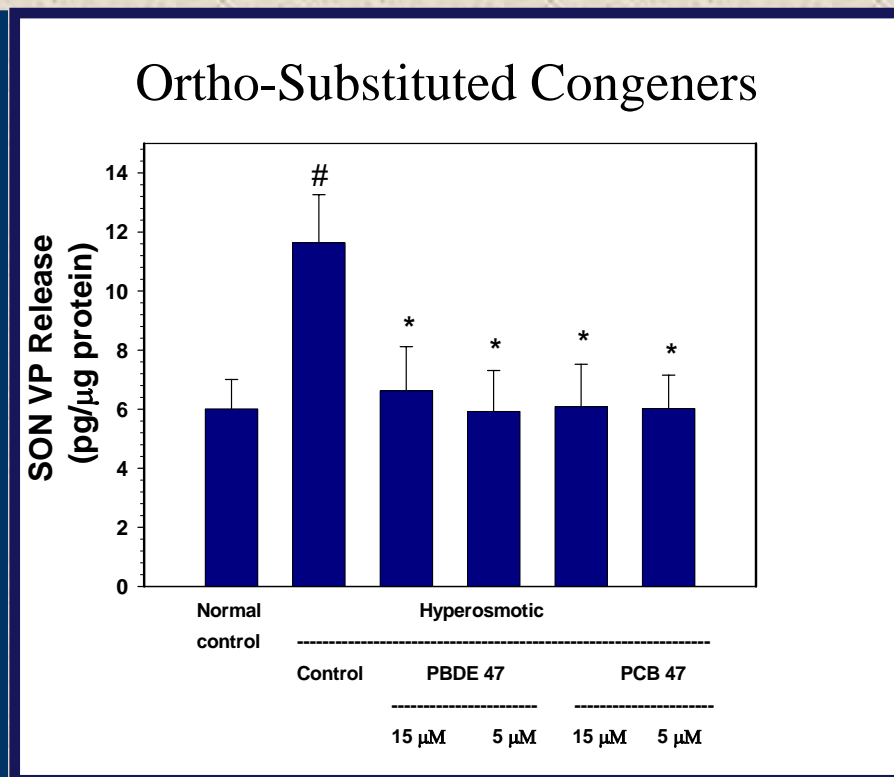
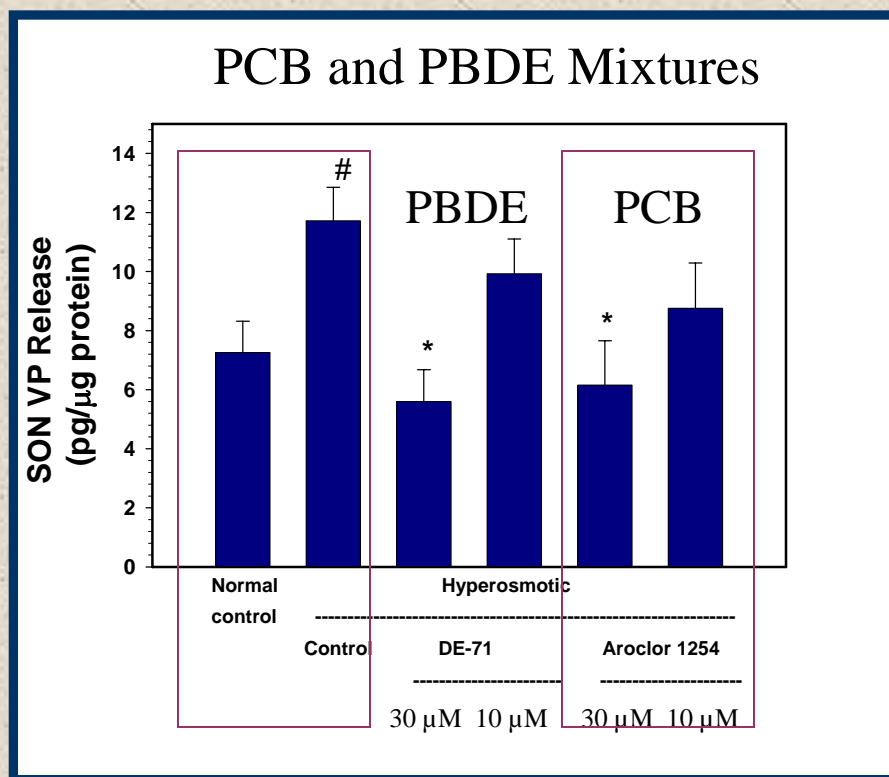
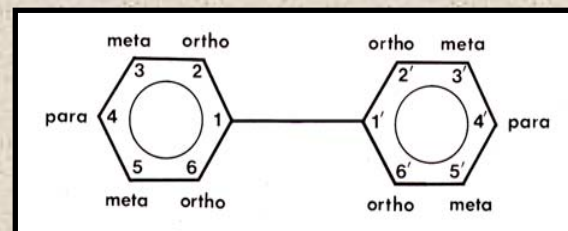
Sacrifice

VP levels in
SON *in vitro*

PCBs suppress stimulated central VP and exaggerate plasma VP



PBDE STUDY: *In Vitro* Application Abolishes Central VP Release

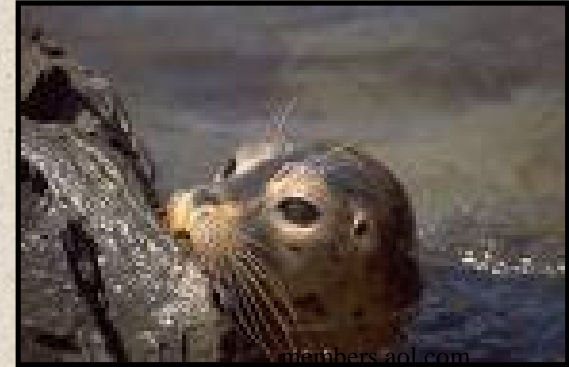


CG Coburn, MC Curras-Collazo and PRS Kodavanti, 2007, Toxicological Sciences (in press)

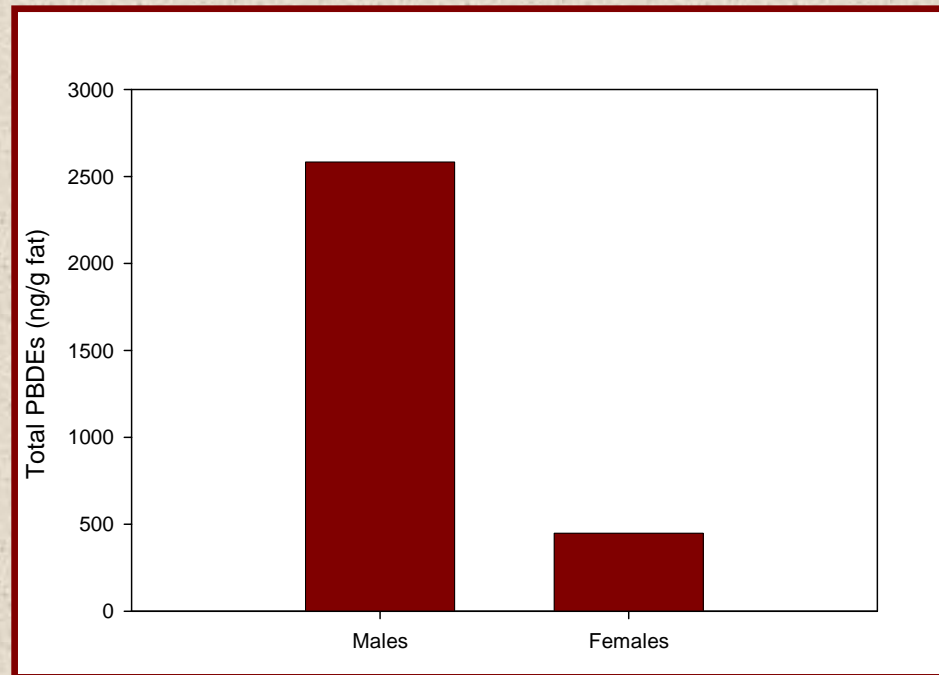
Harbor Seals Bioaccumulate High Levels of PBDEs From San Francisco Bay



www.livingwilderness.com



The average total PBDE concentrations in the males was 2583 (ng/g) which is about 2.6 ppm !



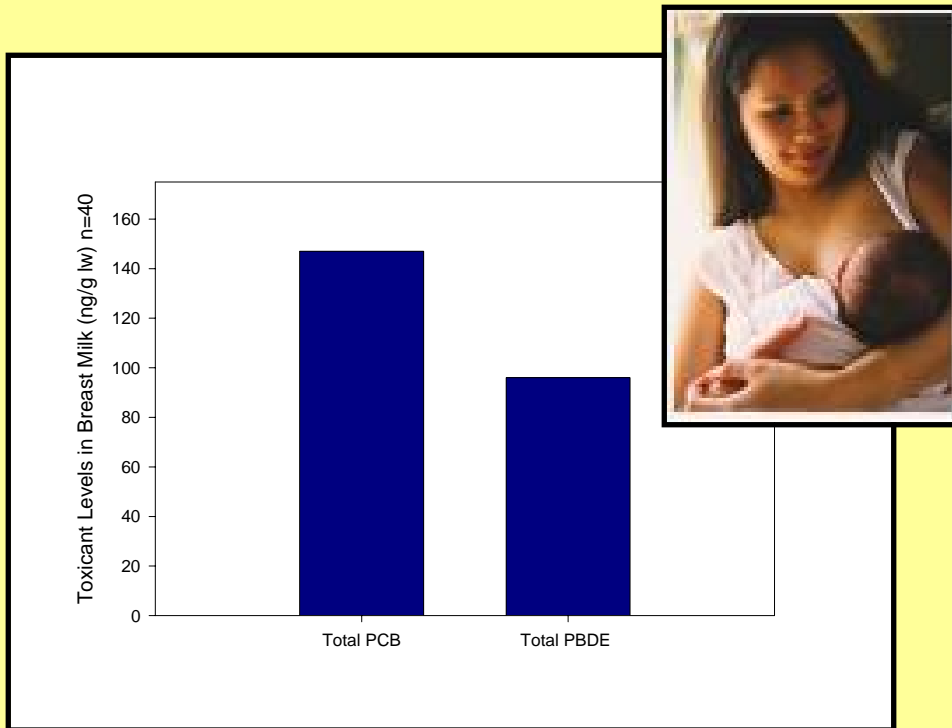
She et al., (2002) Chemosphere 46: 697-707.

Presentation Outline

Part 3. Effects of Perinatal PBDE exposure

Children are at Special Risk

From a sample of 40 first-time mothers from the Pacific Northwest and Canada total PCBs and total PBDEs in breast milk was calculated.



Daily Intake of PBDE:

Adults – 7.7 (ng/Kg b.w.)

Toddlers- 49.9 (ng/Kg b.w.)

Adult Body Burdens:

Blood 64 ng/g lipid wt

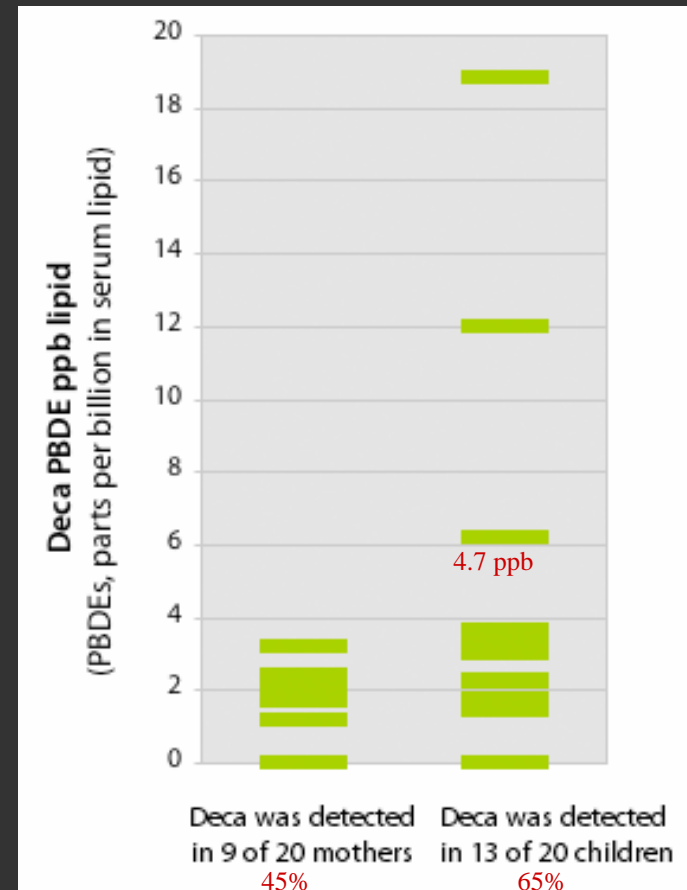
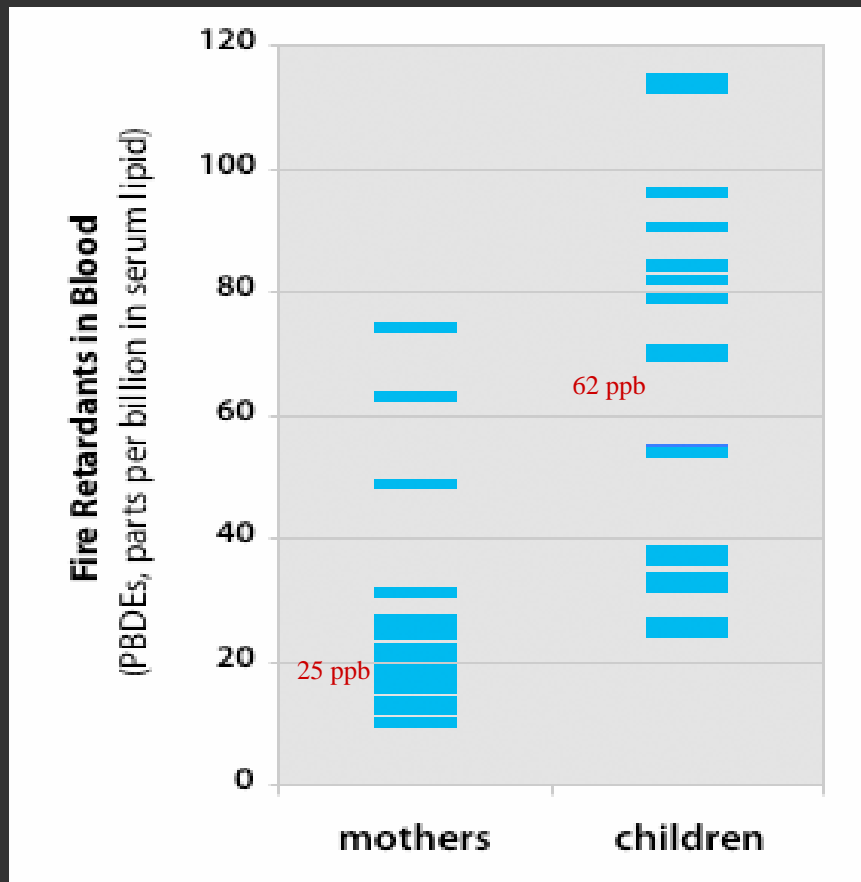
Milk 93.7 ng/g lipid wt.

Lorber, M. (2007) J Expo Sci Environ Epidemiol. (in press)

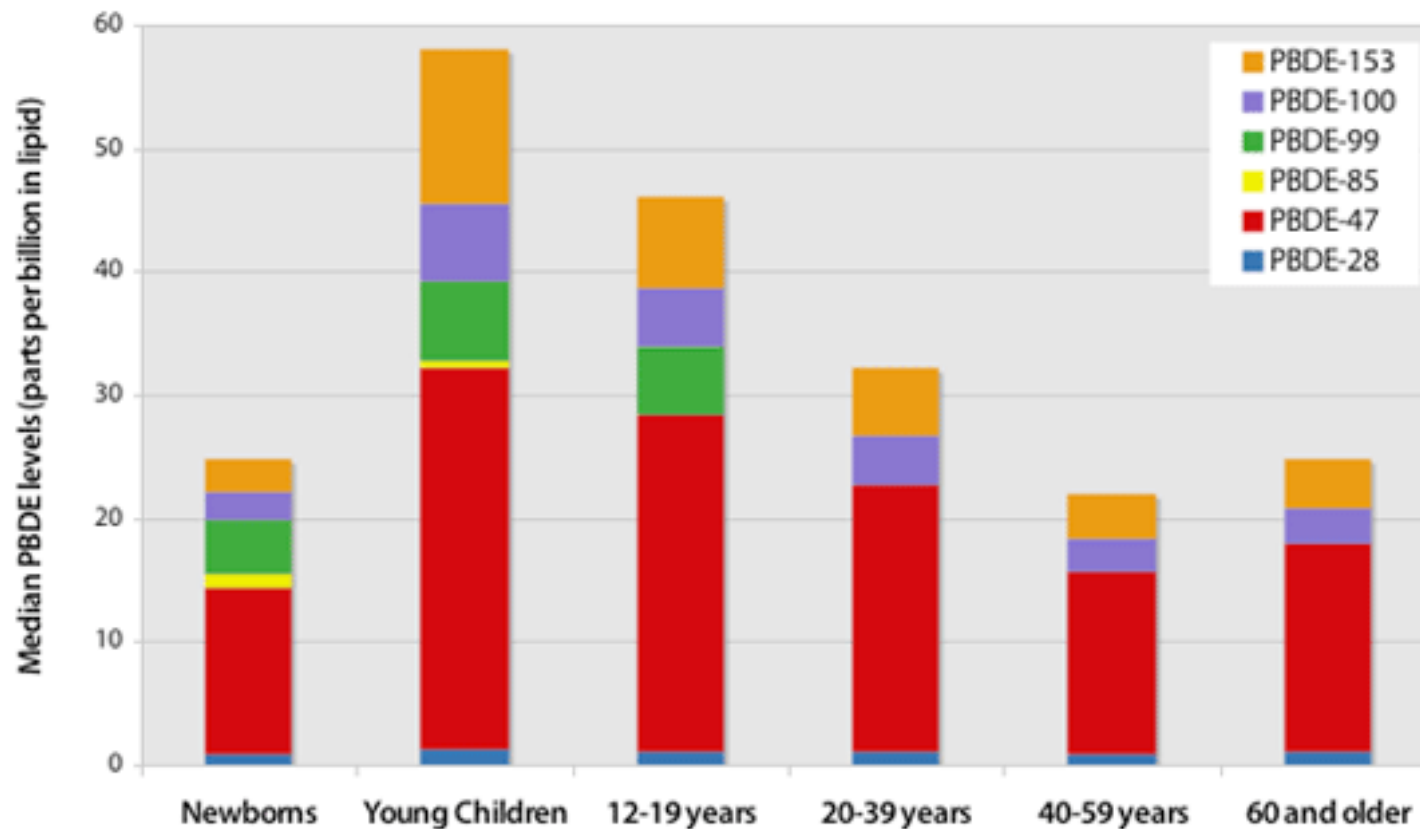
She et al., (2007) Chemosphere 67: S307-S317

Greater incidence and amount of PBDE including Deca congeners in 1-4 yr-old U.S. children vs mothers

20 families from 11 U.S. states
Children were breast fed for at least 4 months



Data from > 2000 persons indicates that young children have nearly 3 X greater body burdens of PBDE



Human Exposure to PBDE

Breast milk



Maternal transfer to fetus



Hand-to-mouth transfer



Diet (esp., fish)



Inhalation of dust (house, office, car, airplane)

Occupation



Perinatal Exposure to DE-71

Oral Gavage Pregnant Dams
DE-71; 1.7 – 30 mg/kg/d, GD 6 – PD 21

14-16 months later

Osmotic challenge

0.9% saline, ip
normosmotic

3.5 M NaCl (6
ml/kg) ip
dehydrated

3-5 hrs *in vivo*

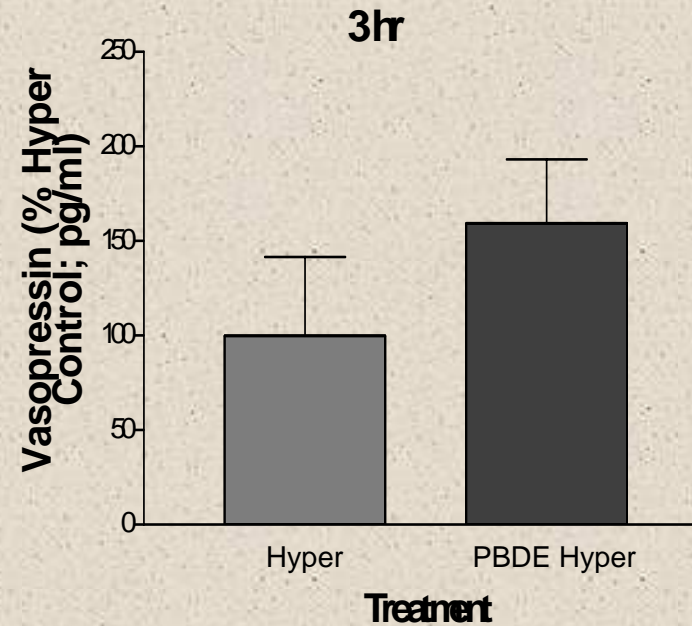
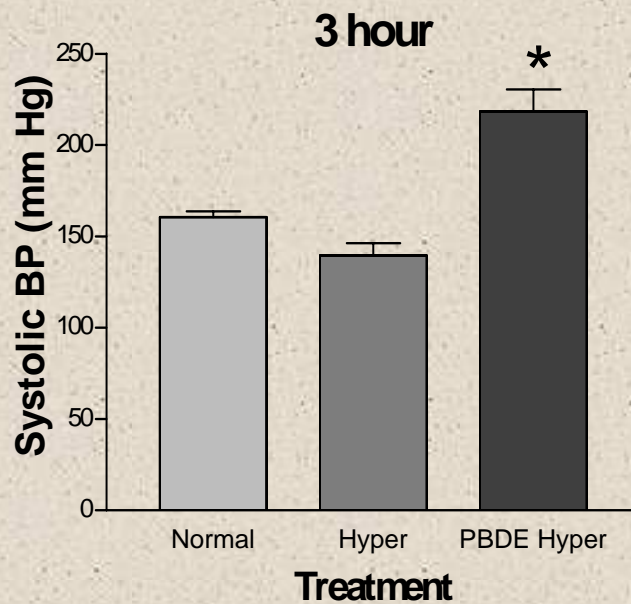
Measure plasma osmolality

Sacrifice

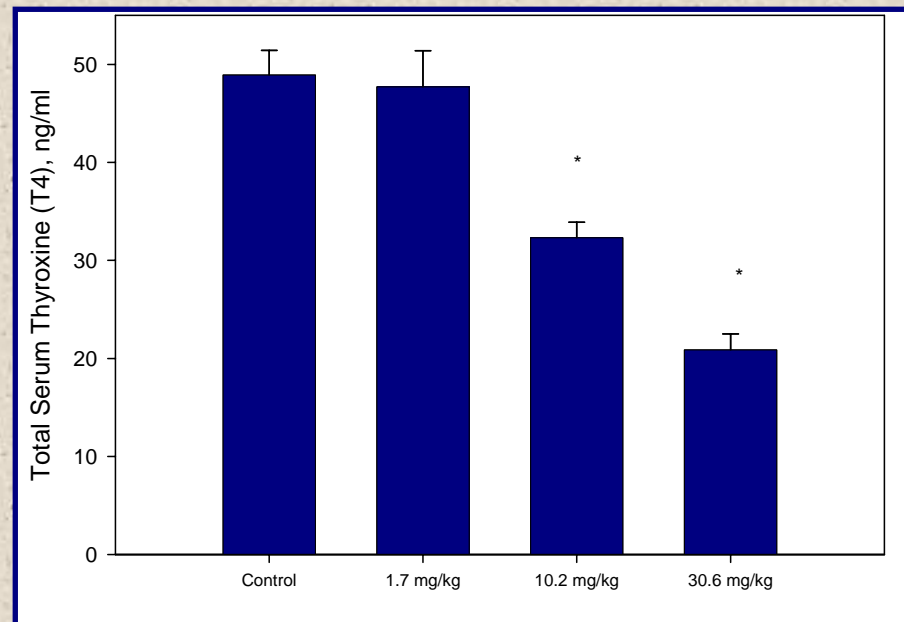
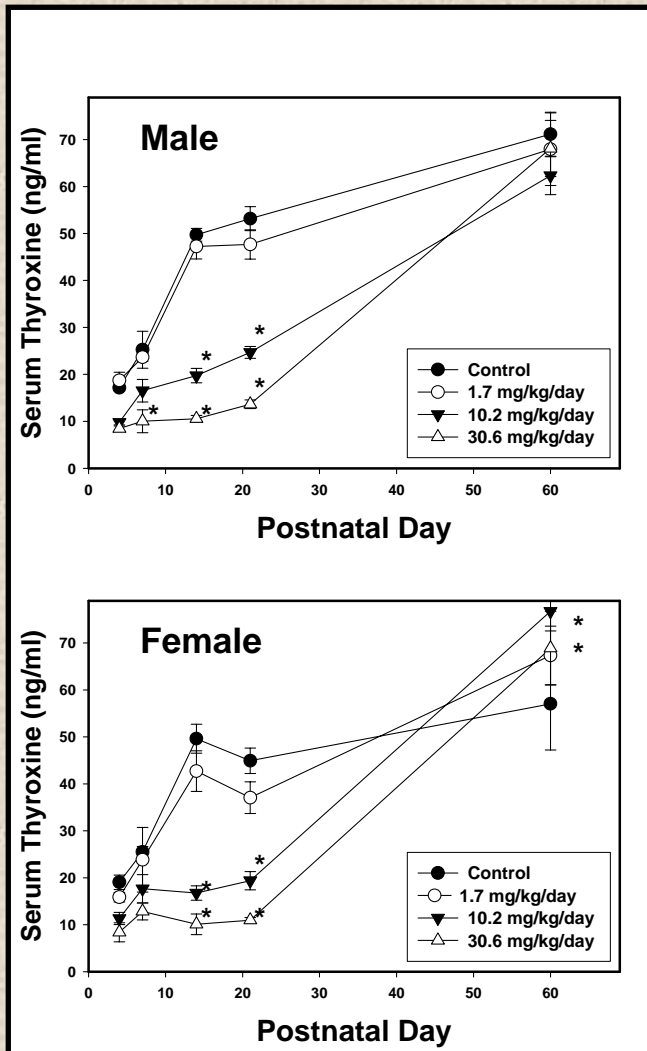
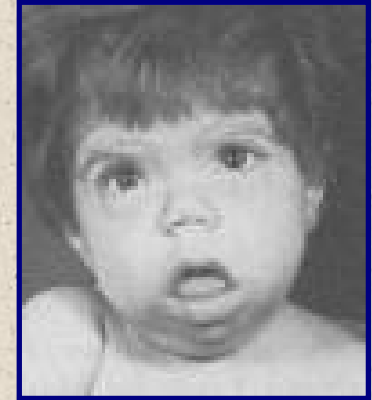
Measure Blood Pressure
Plasma Osmolality
Plasma Vasopressin

Perinatal PBDE exposure alters osmoregulation and blood pressure in aged rats

	30 Minute Normosmotic	3 Hour Normosmotic	30 Minute Hyperosmotic	3 Hour Hyperosmotic
Treatment None	300.3±2.1 (N=4)	301.2±2.0 (N=4)	338.5±8.6 (N=7)*	343.1±6.9(N=8)*
Lo PBDE			345.0±10.7 (N=4)*	362.0±12.1 (N=4)*
High PBDE			325.1±11.4 (N=4)*	367.4±11.9 (N=3)*#
Combined Lo and High PBDE			335.06±8.2 (N=8)	364.33±8.0 (N=7)*,#,\$



Perinatal Exposure to the Industrial PBDE Mixture (DE-71) Induces Transient Hypothyroidism



CG. Coburn and PRS. Kodavanti Unpublished Data

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Collaborators:

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City, Mexico
Dr. Q. Pittman and L.Bauce, Department of Physiology &
Biophysics, University of Calgary, Alberta, Canada

Funding Sources



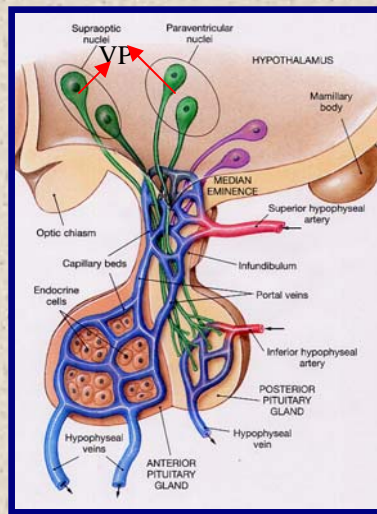
Vasopressin is a Busy Molecule !

As a hormone it is transported to axon terminals in the posterior pituitary gland, is released into circulation and acts upon the kidney to promote water retention and on resistance blood vessels to increase blood pressure.

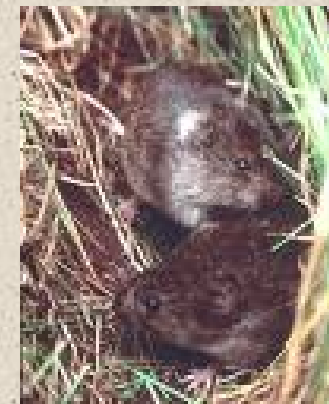
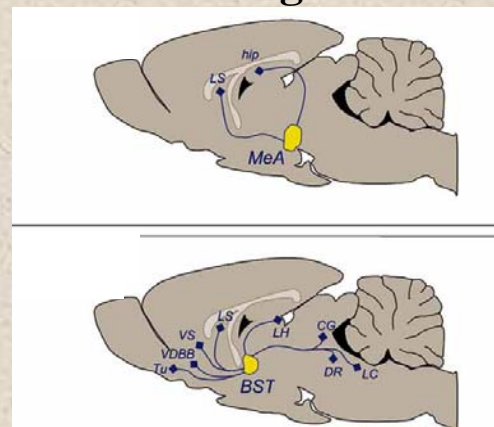


www.umm.edu

As a neuropeptide vasopressin acts within the supraoptic nucleus to autoregulate its own release.



As a neurotransmitter and neurohormone vasopressin acts on various brain regions to participate in processes such as learning, memory and social bonding.



Ring, R. Curr. Pharm. Des. 11: 205-225, 2005

www.science.smith.edu