

# **Neurobiology of Aggression and Violence: Systems, Intervention, and Impact**



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# Lecture Outline

## 1. Overview

## 2. Regulatory Systems

a. hormones

b. neurotransmitters

c. interactions

## 3. Intervention and Imaging

## 4. Aggression as a Model for Disease

a. stress-related affective illness

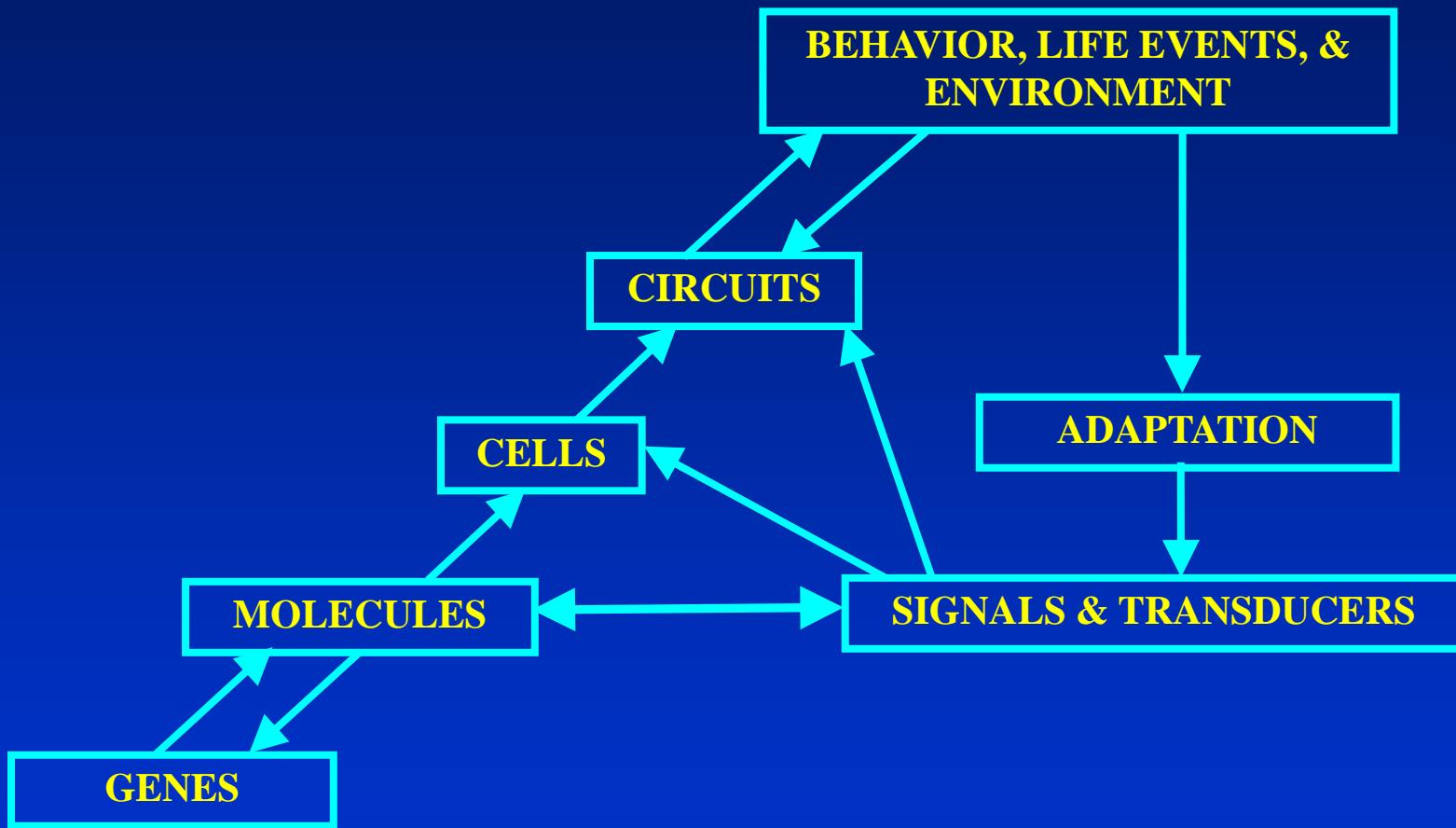
## 5. Summary and Conclusions

# Economic Burden

➤ Violent Offenses	\$70 billion
➤ Stress-Related Affective Illness	\$150 billion
➤ Dementias	\$135 billion
<b>TOTAL</b>	<b>\$355 billion</b>



# Aggression and Violence: A Systems Perspective



## Genetics: One Gene Models

**Witkin et al (1976).** Criminality in XYY and XXY men. **Science**

**Brunner et al. (1993)** Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. **Science**

**Saudou et al. (1994).** Enhanced aggressive behavior in mice lacking 5-HT<sub>1B</sub> receptor. **Science**

**Nelson et al. (1995).** Behavioural abnormalities in male mice lacking neuronal nitric oxide synthase. **Nature**

**Ogawa et al (1997).** Behavioral effects of estrogen receptor gene disruption in male mice. **PNAS**

**Merriman, Cameron (2007).** Risk-taking: behind the warrior gene story. **NZ Medical Journal**

***Complex Social Behaviors Integrate Multiple Gene Pathways: Neurogenomics***

# Definitions

## ➤ Conspecific Aggression

- Part of reproduction
- Establishment of dominance status
- Access to Resources

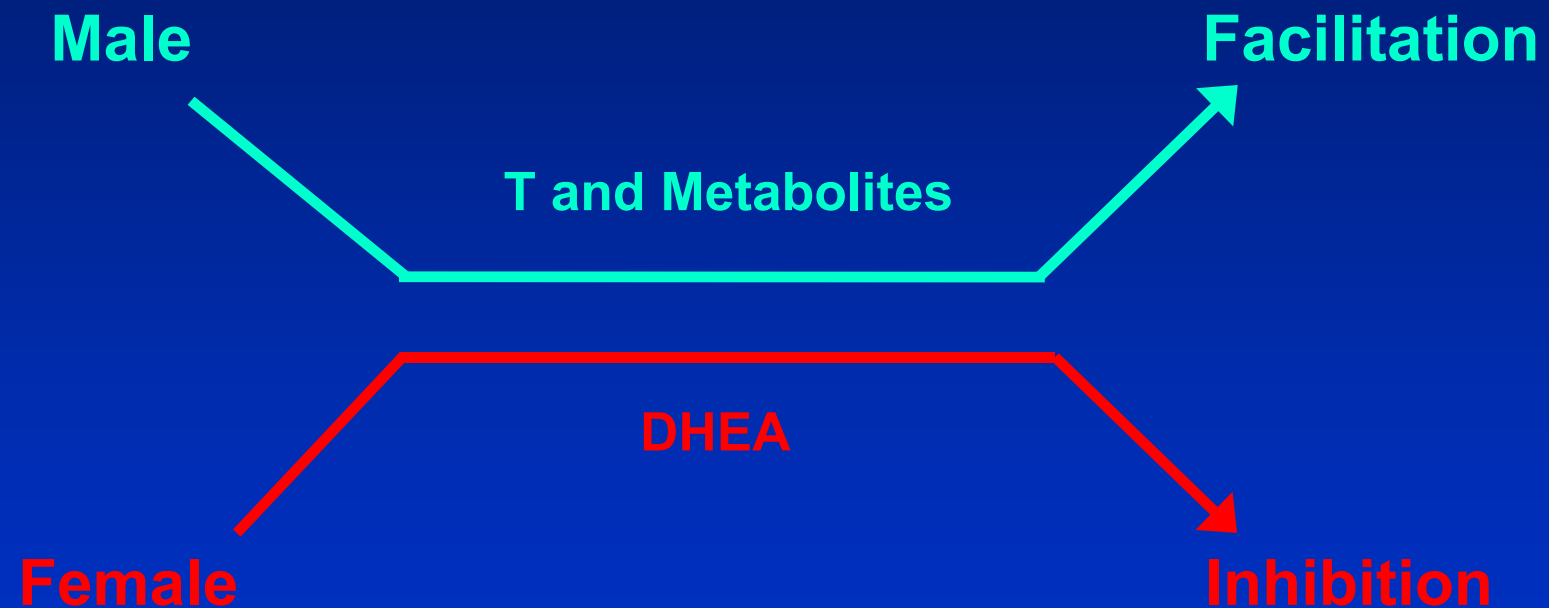


## ➤ Violence/Inappropriate Aggression

- Intent to harm and cause injury
- Assault, murder

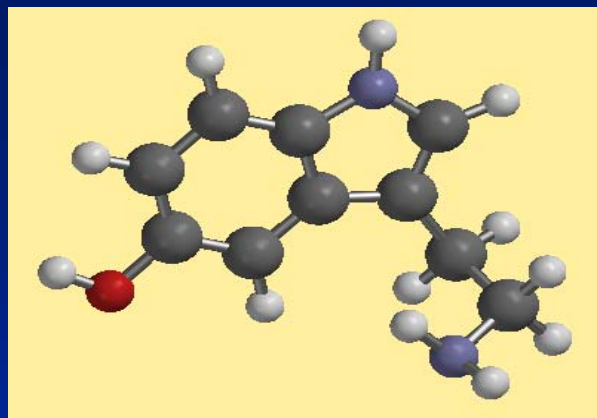


# Neurobiological Regulatory Systems: Sex Differences

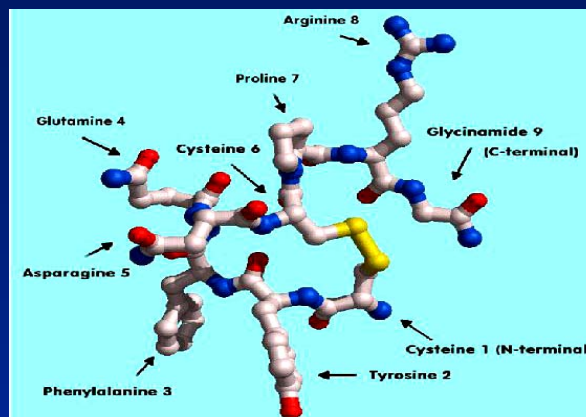


# Target Signaling Systems

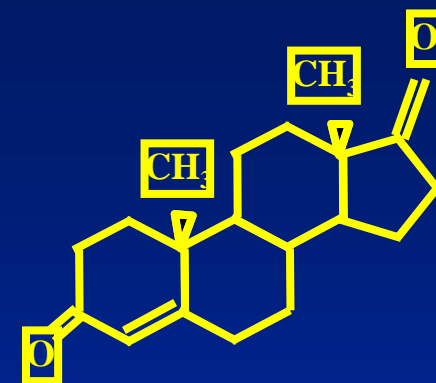
M  
A  
L  
E



5-HT

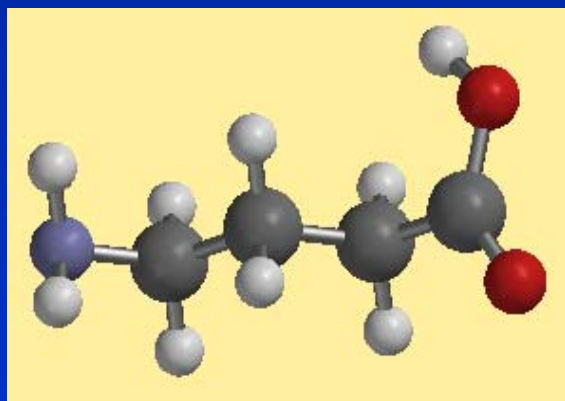


AVP

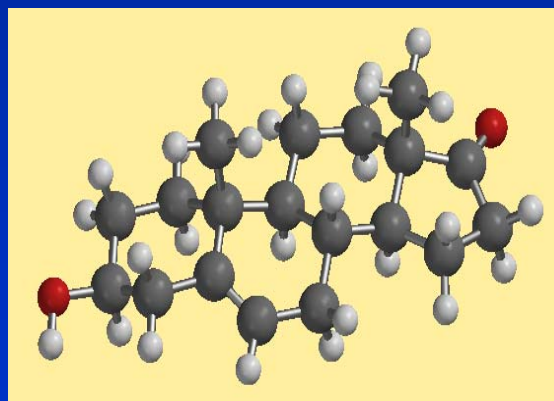


TESTOSTERONE

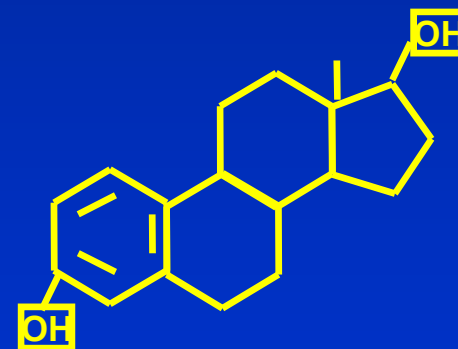
F  
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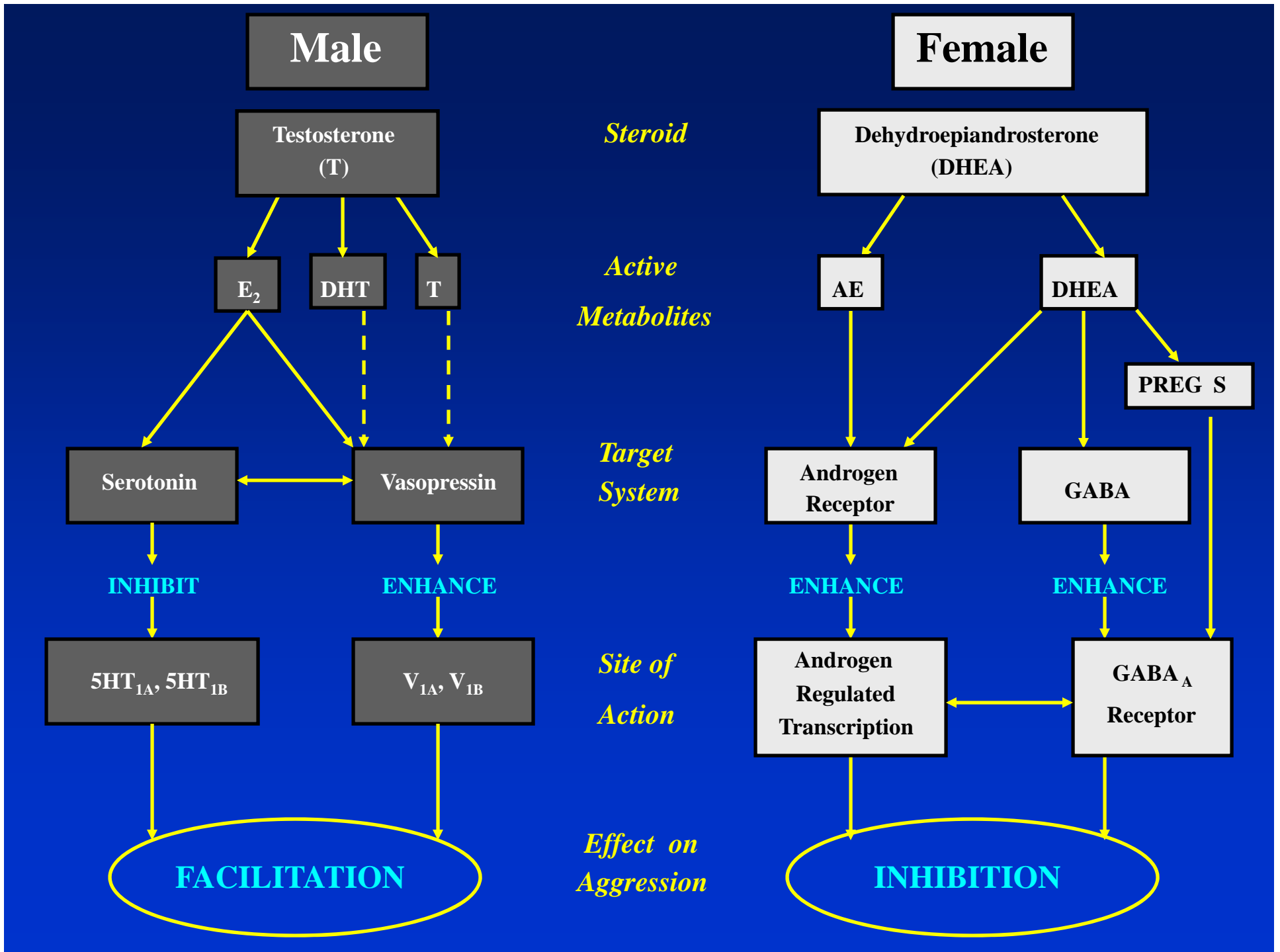
GABA



DHEA



ESTRADIOL



# Hormonal Hypotheses

- **Causal:** *invariant and it's all about testosterone*
- **Facilitative:** *a probabilistic model*
- **Neuromodulator:** *integrates endocrine, peptidergic, & neurochemical systems*



# MALES

## ➤ Hormones

- testosterone
- estradiol

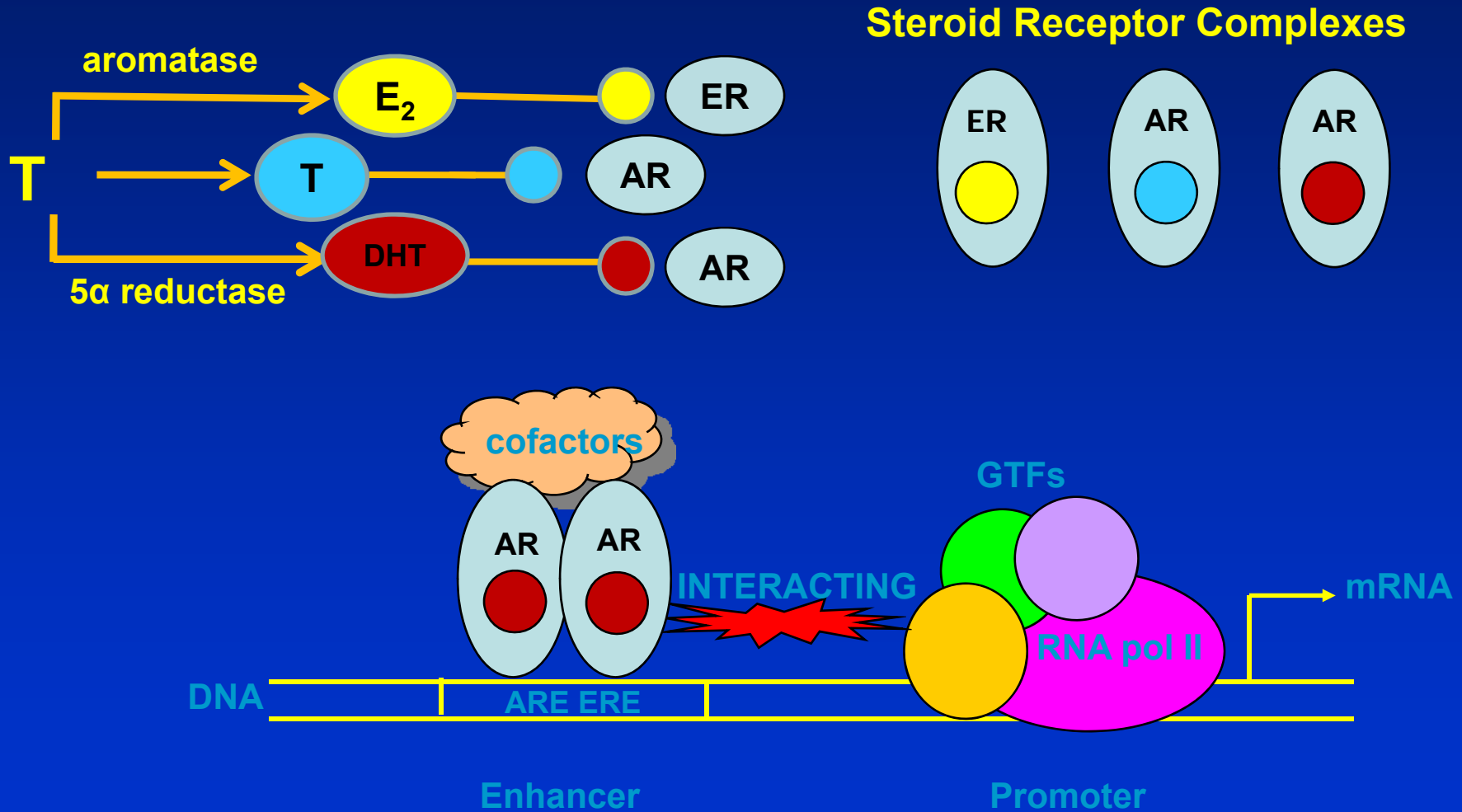
## ➤ Neurotransmitters

- serotonin
- vasopressin



# Genomic Effects of Testosterone

- Metabolism and Steroid Receptors Determine Effects in Target Neurons



# Neuroendocrine Regulatory Systems for Intermale Aggression



Androgen  
Sensitive

Estrogen  
Sensitive

Combined or  
Synergistic

Direct  
T

Male

++

++

++

++

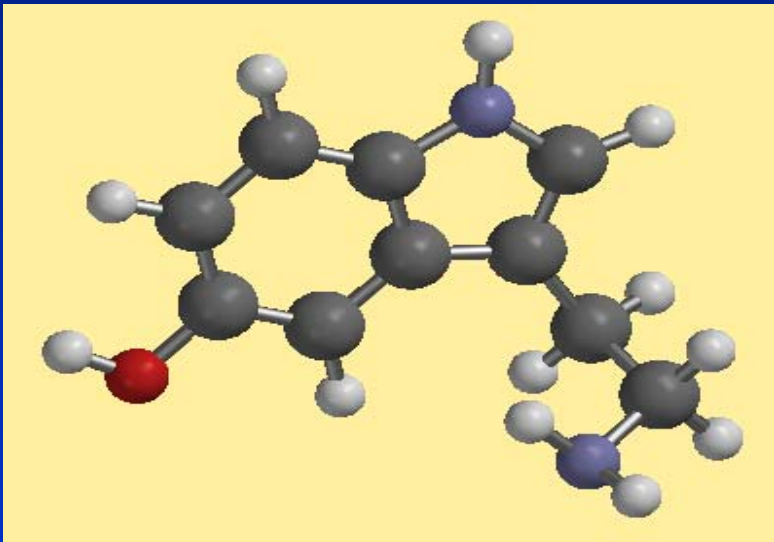
++ high sensitivity

+ moderate sensitivity

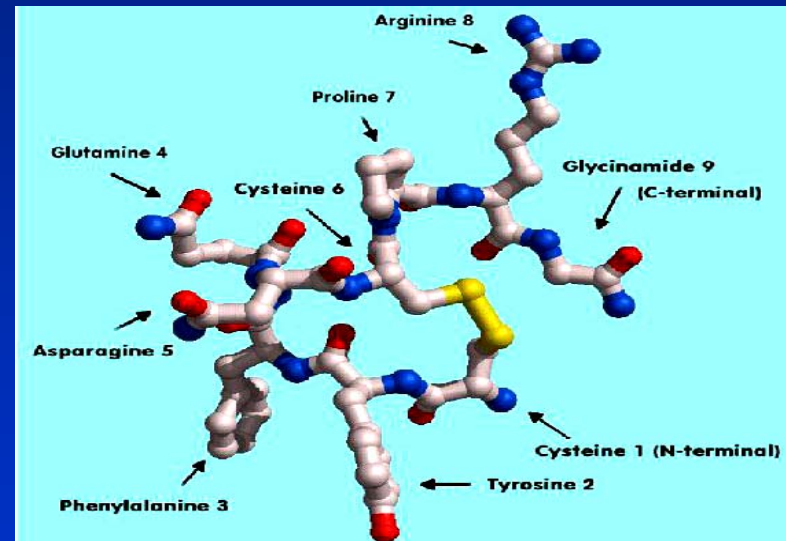
- insensitive



# Neurotransmitters



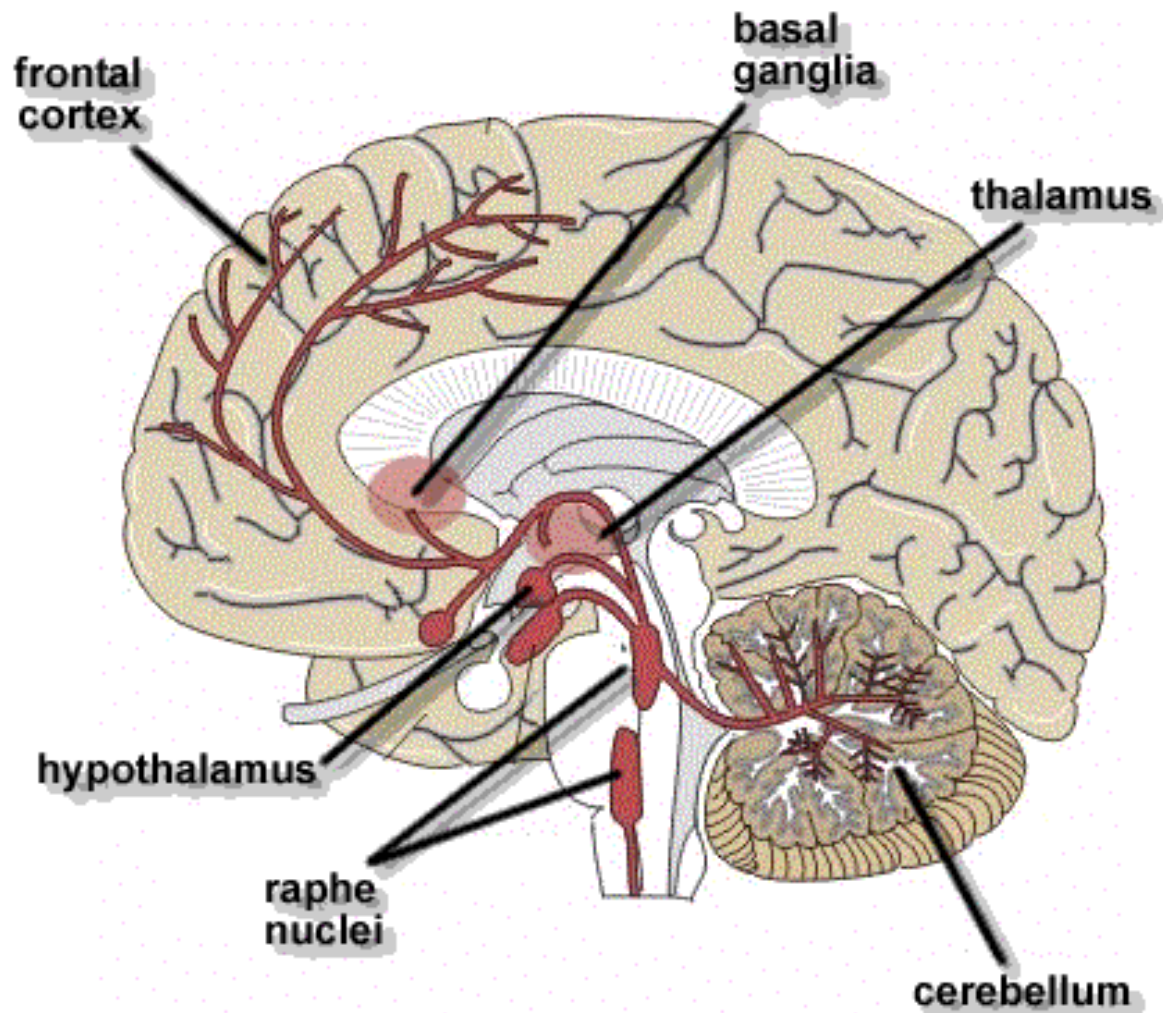
**5HT**



**AVP**

# Serotonin System: Human Brain

The serotonergic system consists of ascending axons from cell bodies in the raphe nuclei



# Serotonin and Aggression

## ➤ Inhibitory

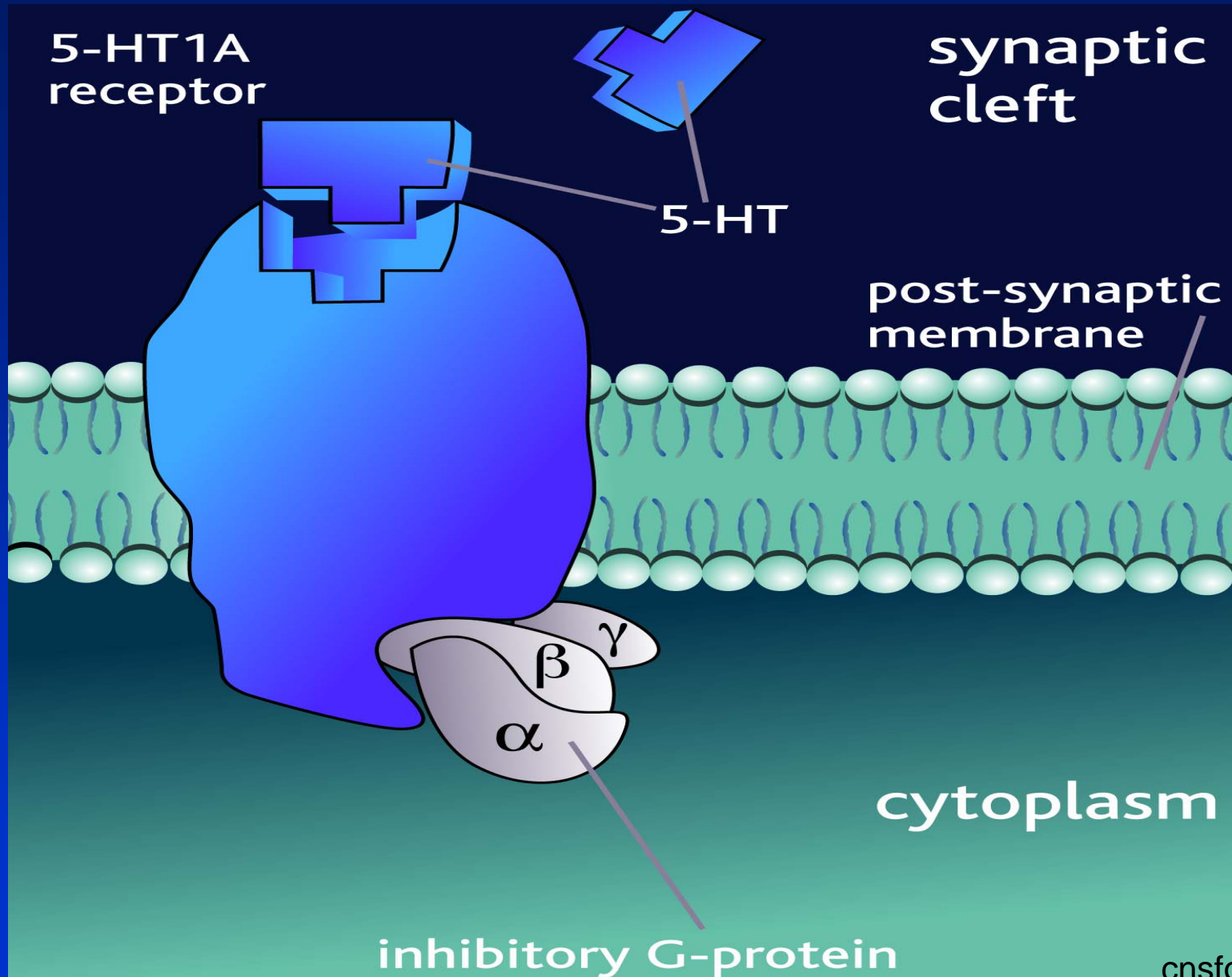
**Pharmacology: 5HT1a and 5HT1b receptor**

**Genetics: Knockout Mouse**

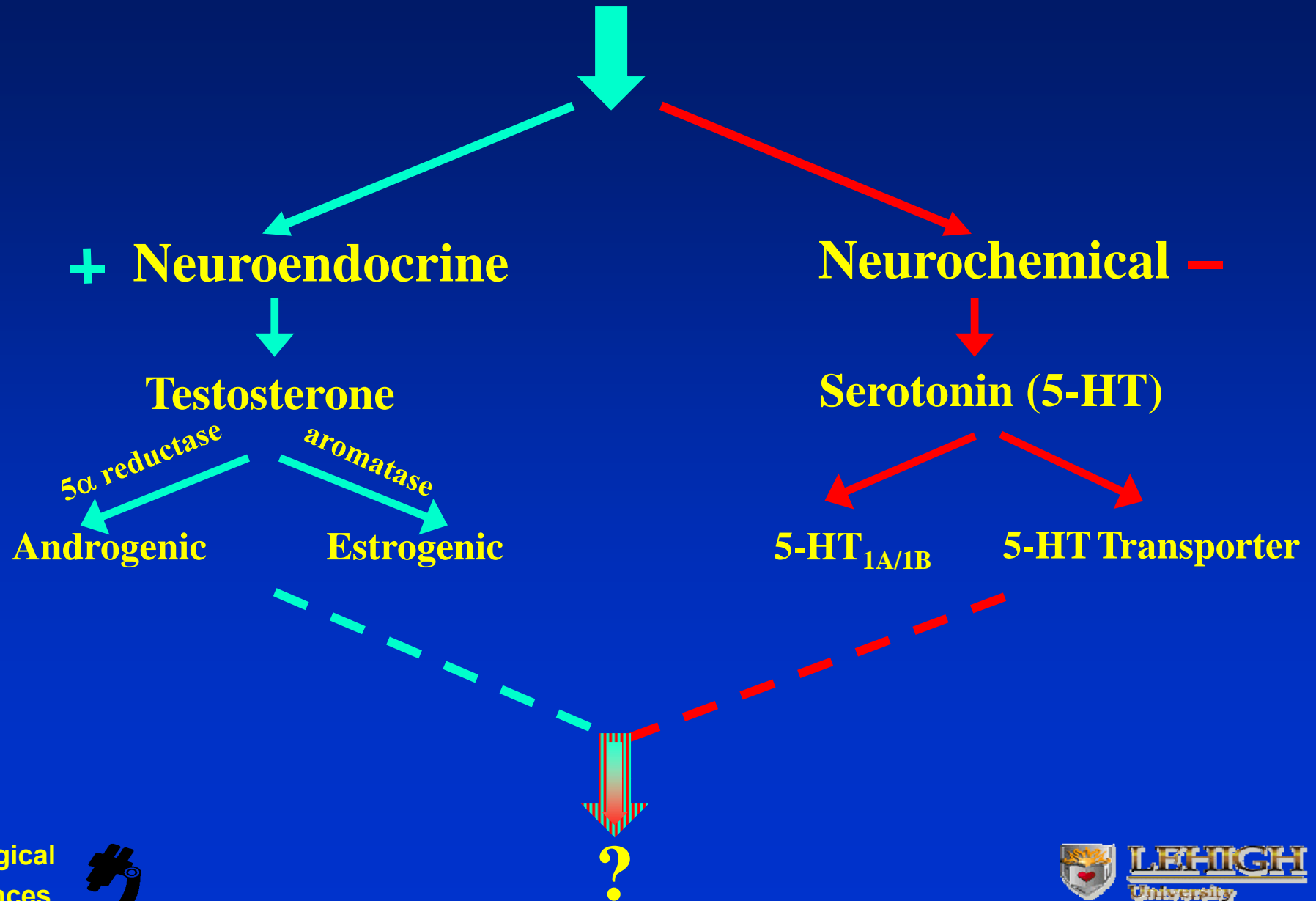
**Human Impulsivity and Hostility**

***THERE IS AN INVERSE RELATIONSHIP BETWEEN  
SEROTONIN FUNCTION AND AGGRESSION***

# Serotonin 1a Receptor



# Signal Integration: Testosterone and Serotonin

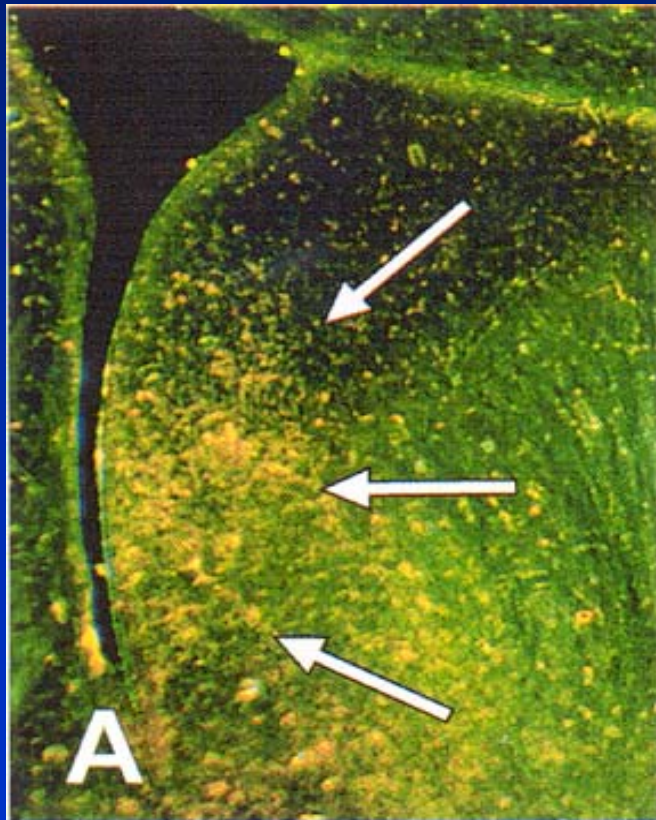


# Vasopressin: A Facilitator of Aggression

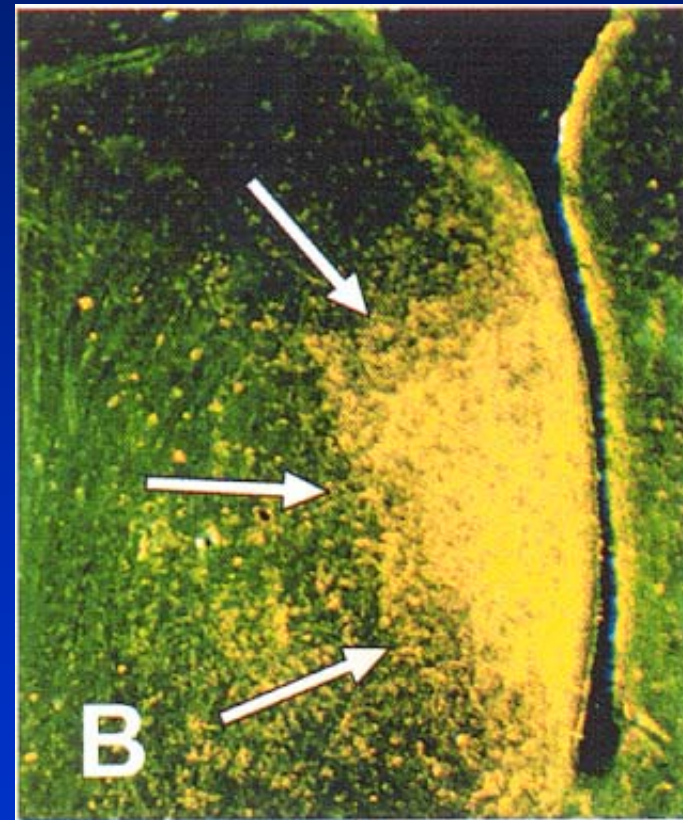
- Established link to aggression
- Testosterone Dependent
- Interface with serotonin system



# Sexual Dimorphism in Vasopressin Fibers in Rat Lateral Septum



**Female**



**Male**

# Vasopressin: Biological Diversity

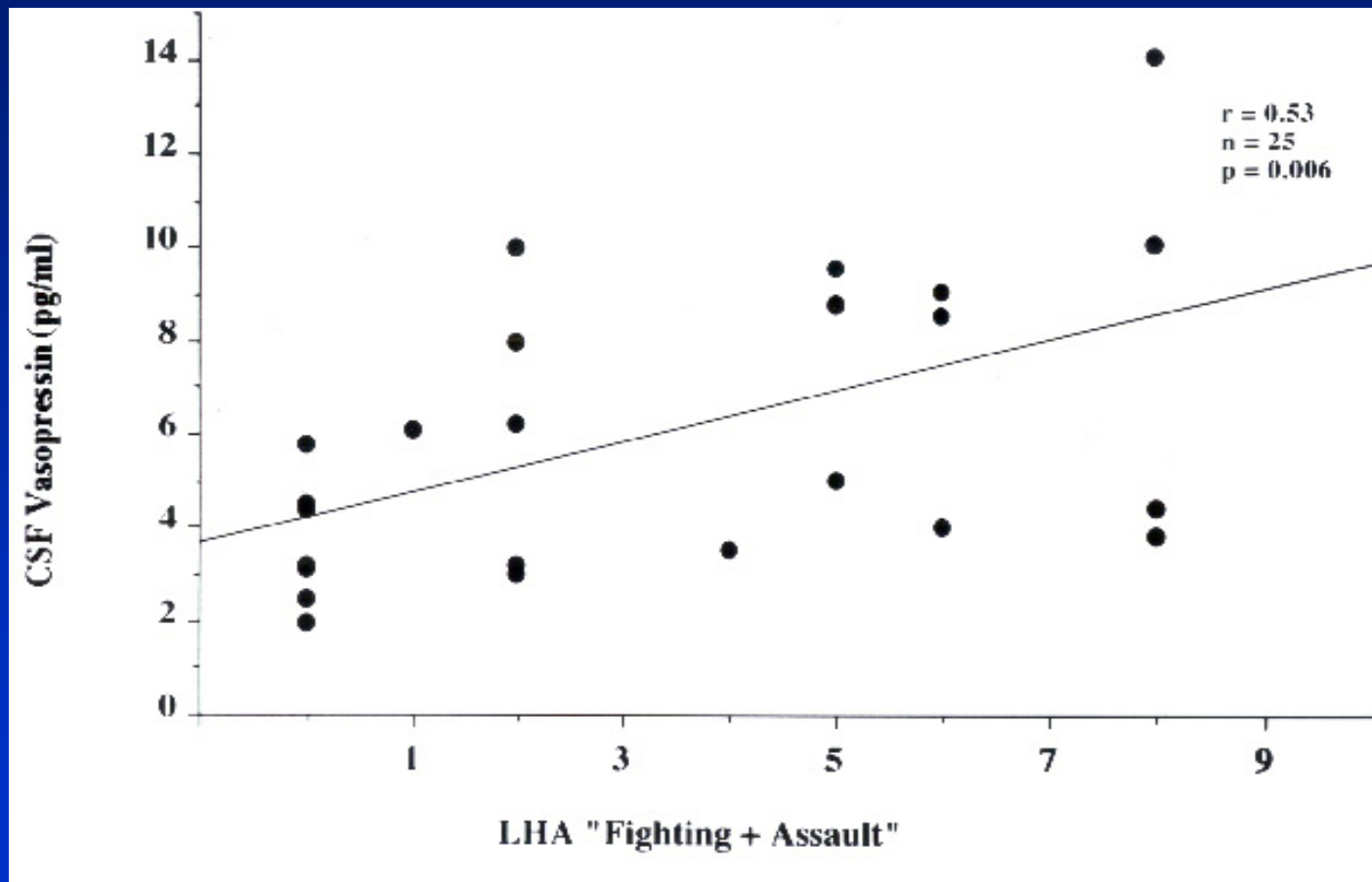
## Invertebrate & Vertebrate Physiology

- fluid regulation
- carbohydrate metabolism
- thermoregulation
- reproductive function

## Vertebrate Behavior

- communication
- sexual behavior
- paternal/maternal care
- pair bonding
- social memory
- aggression
- stress-related disorders

# Patients with Violent Personalities Have Blunted Serotonin Activity and Elevated CSF Vasopressin

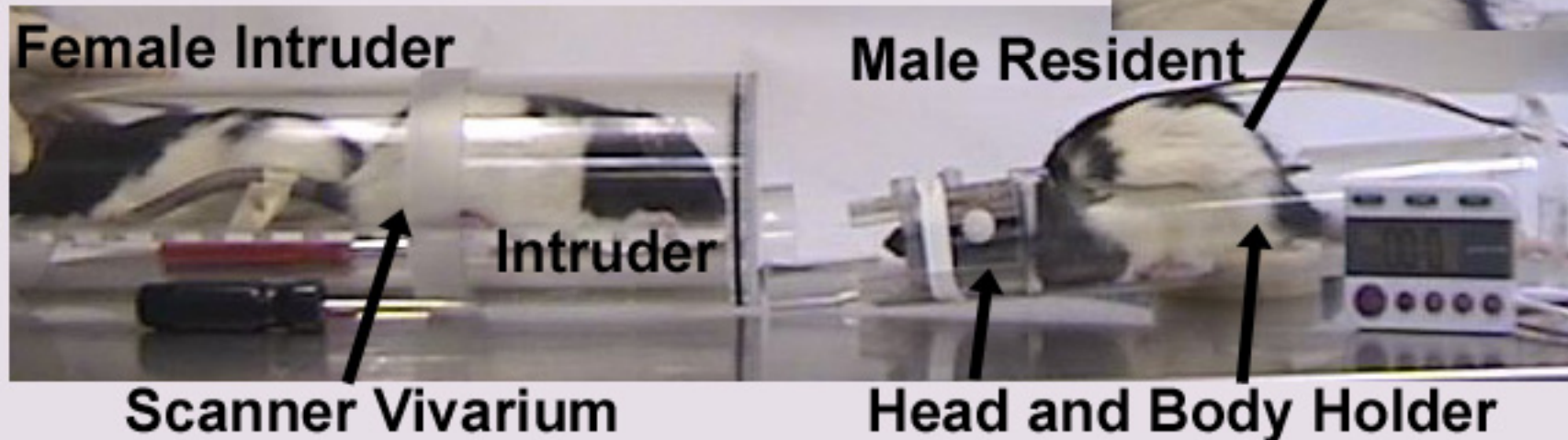


# Imaging and Intervention



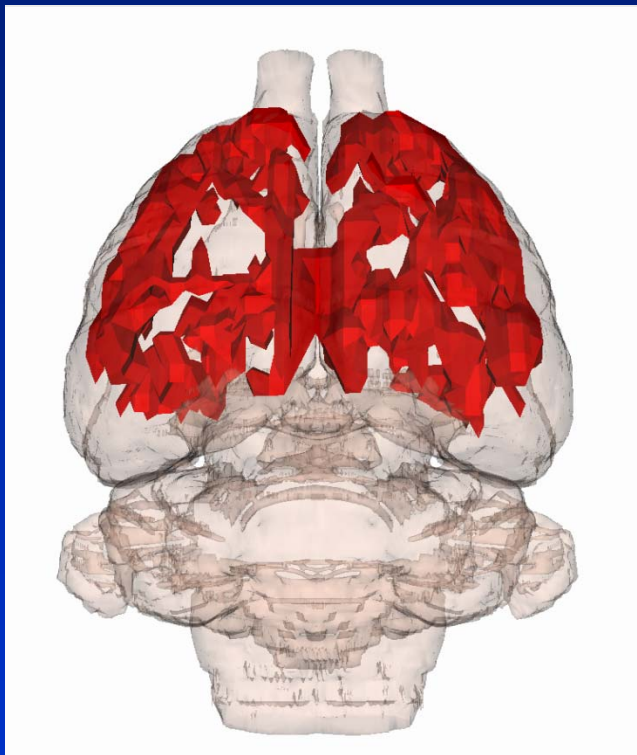
# fMRI: Imaging Social Arousal and Aggression

## Resident/Intruder Interaction in the Imaging Environment

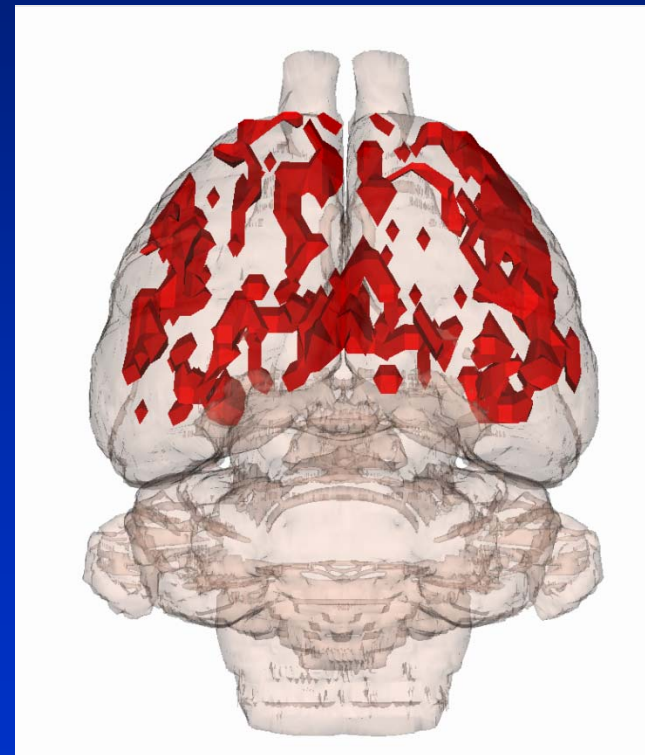


# Vasopressin 1a Antagonism Blocks Aggression

Social Stress/Arousal in Response to an Intruder Male



Activated Pathway



After Oral SRX251

# Vasopressin 1a Antagonism Blocks Aggression

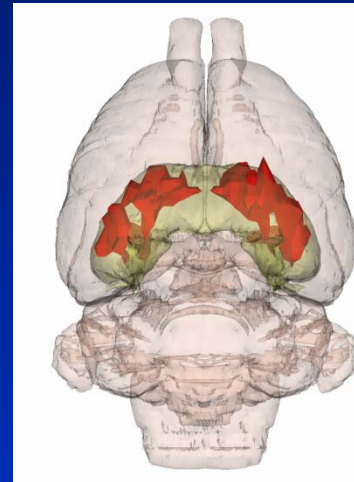
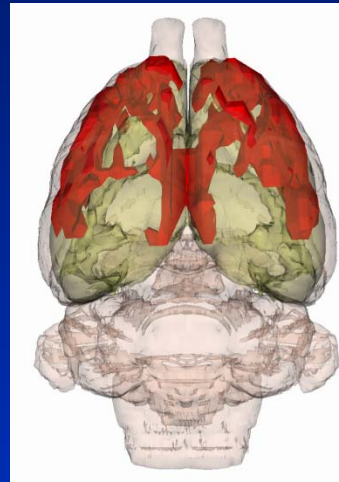
Amygdala

Cortex

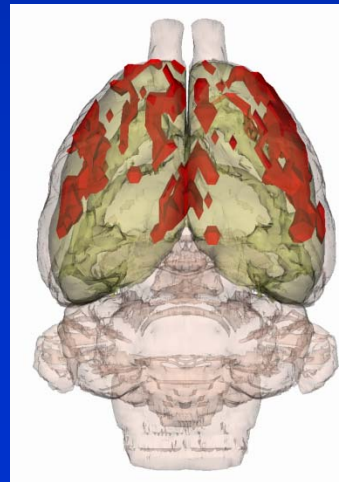
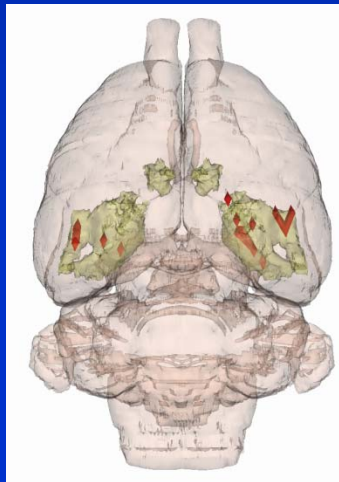
Hippocampus

Thalamus

Mate & Intruder



SRX251 Treatment



# Summary

- **Testosterone and its metabolites maintain AVP fibers and V1a receptor integrity**
- **Vasopressin receptor antagonists may represent a novel intervention strategy for inappropriate aggression and stress-related indications**



# Aggression as a Model for Stress-related Affective Illness



# Social Subjugation/Chronic Defeat: Physiological Effects & Consequences

- Cortisol dysregulation
- Conditioned defeat
- Testosterone suppression
- AVP suppression
- 5HT hyperactivity
- Biogenic amine changes

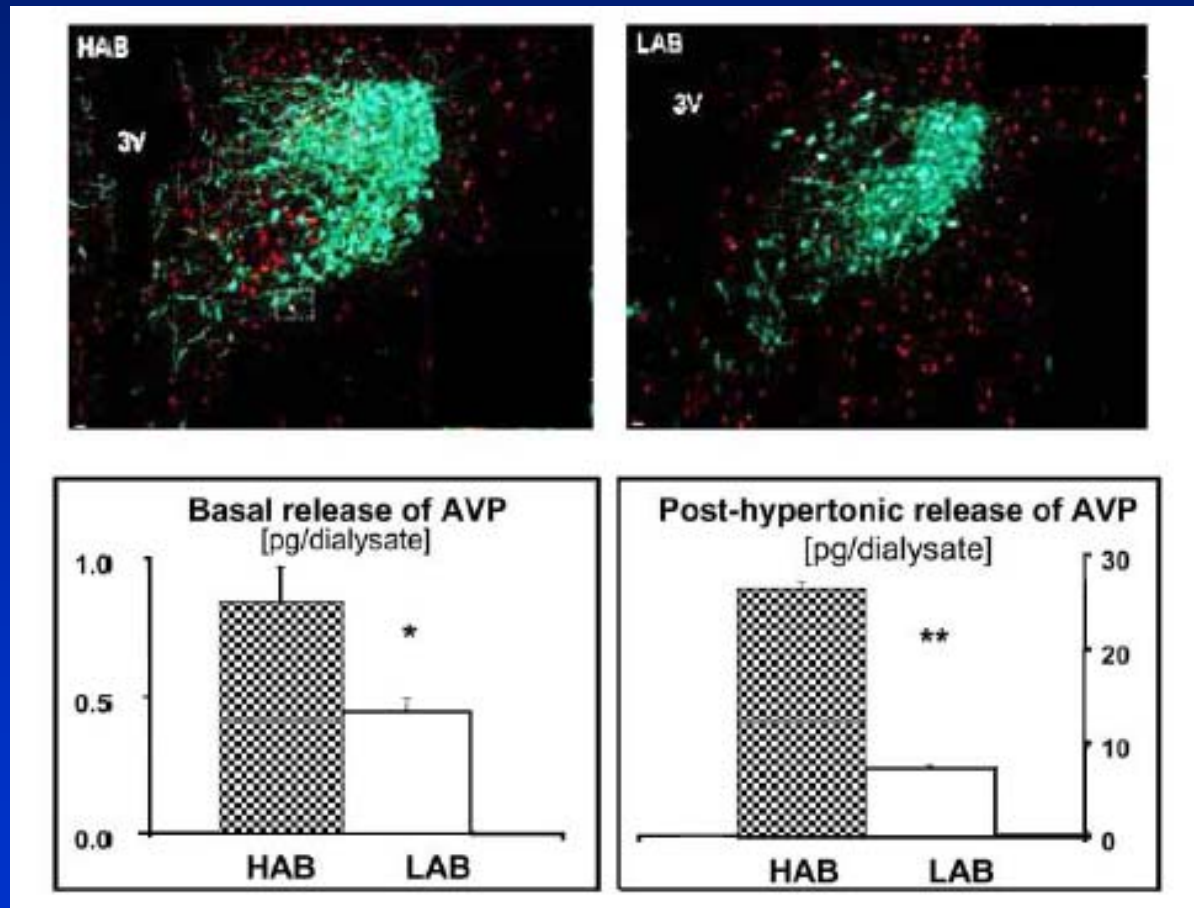


- Depression
- Anxiety
- Heart Disease
- Immune Compromise



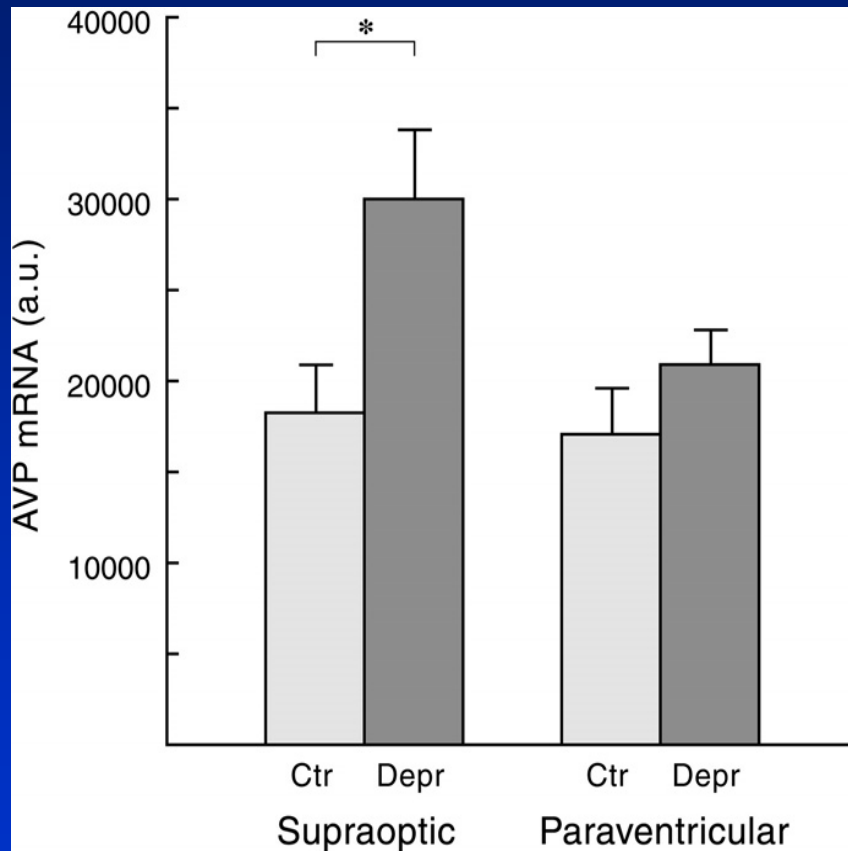
# Vasopressin is Linked to Stress-related Disorders

R. Landgraf (2006). Involvement of the vasopressin system in stress-related disorders. *CNS & Neurological Disorders – Drug Targets* 5, 167-179

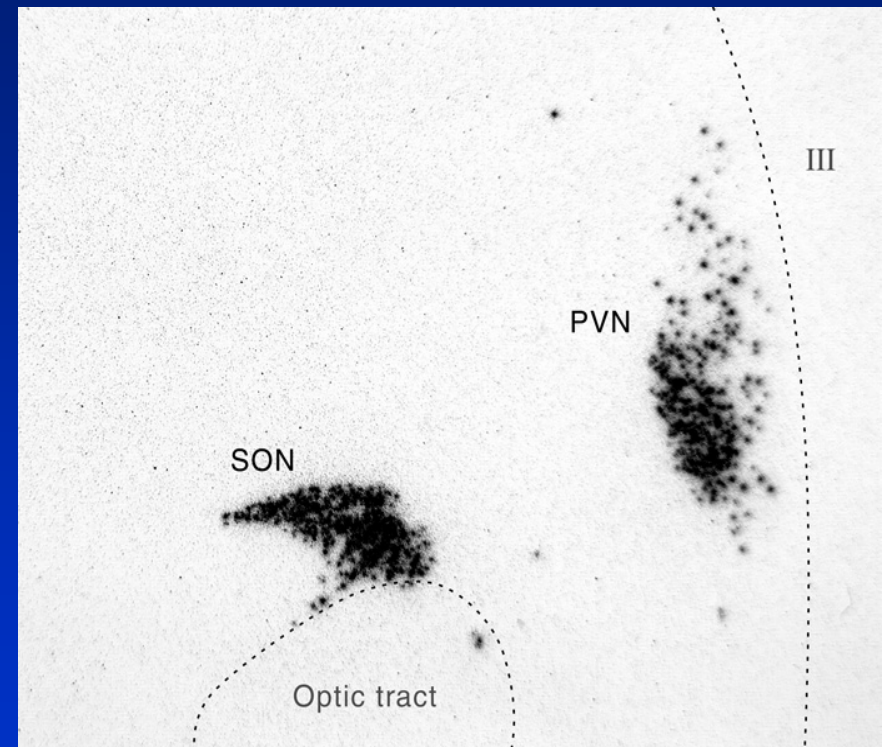


Synthesis, content, and release of AVP in PVN in HAB and LAB rats under basal and stress conditions

# AVP mRNA in Supraoptic and Paraventricular Nuclei from Depressed and Control Individuals

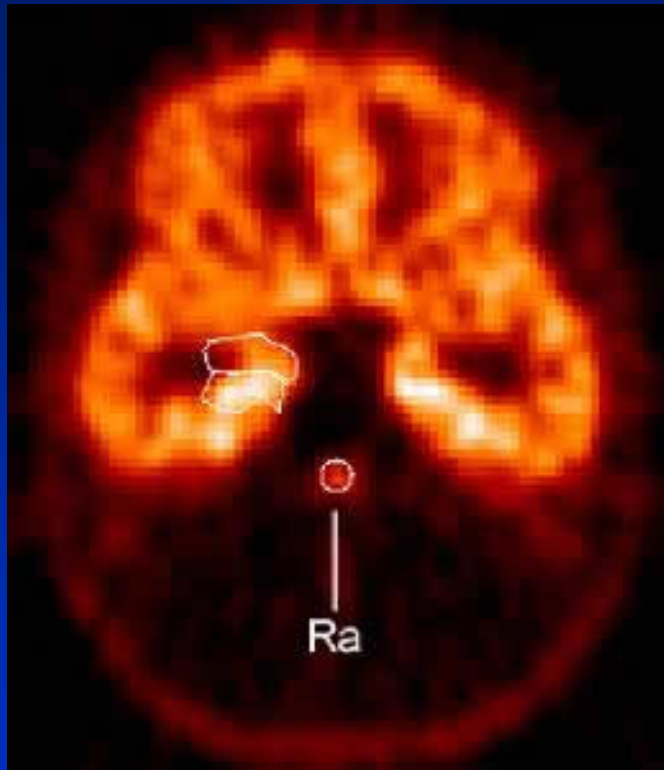


AVP mRNA in PVN and SON in depressed (n=9) and control patients (n=8)

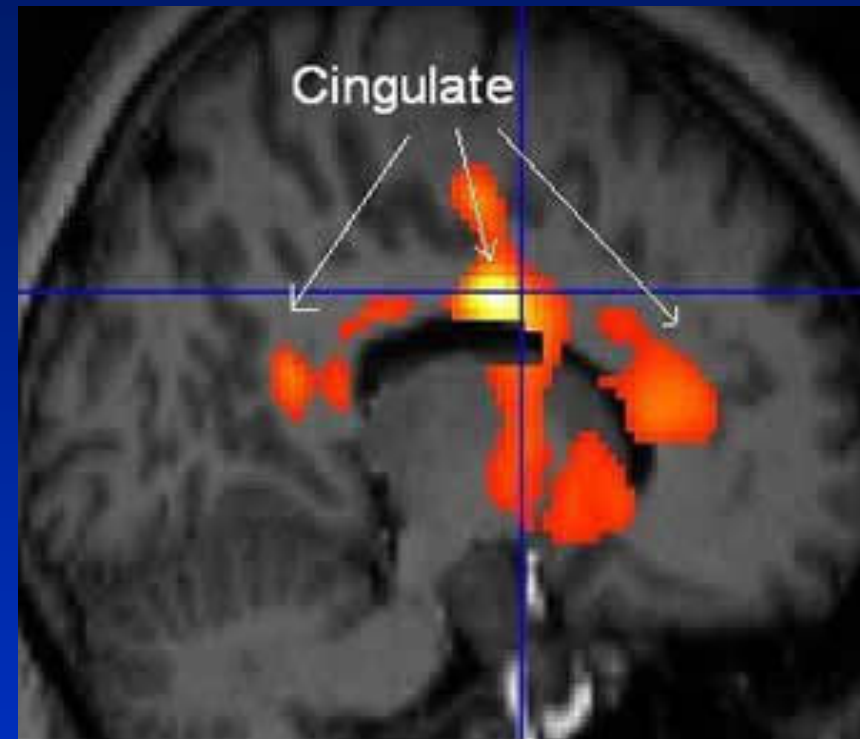


Signal on film in SON and PVN

# Panic Disorder and 5HT1a Receptor



PET scan shows distribution of serotonin 5-HT1A receptors (front of brain is at top), which were reduced by about a third in the raphe (Ra) in panic disorder patients.



Statistically-analyzed PET scan data superimposed on structural MRI scan (front of brain is at right) shows areas in the anterior and posterior cingulate where panic disorder patients had nearly one third fewer serotonin 5-HT1A receptors compared to healthy control subjects. The lighter the color, the greater the difference between patients and controls.

# Summary: Animal Models and Human Psychopathology

- Chronic subjugation disrupts conspecific aggression
- Physiological changes in hormonal and neurochemical function mimic stress-related disorders
- Balance between AVP/5-HT is critical



