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

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Outline: Goals

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. Aging and Diet
    a. supplements
    b. impact on aggression and impulsivity
    c. neurogenomics
6. Summary and Conclusions

Genetics: One Gene Models

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

Saudou et al (1994). Enhanced aggressive behavior in mice lacking 5-HT1B receptor. **Science**

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

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

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

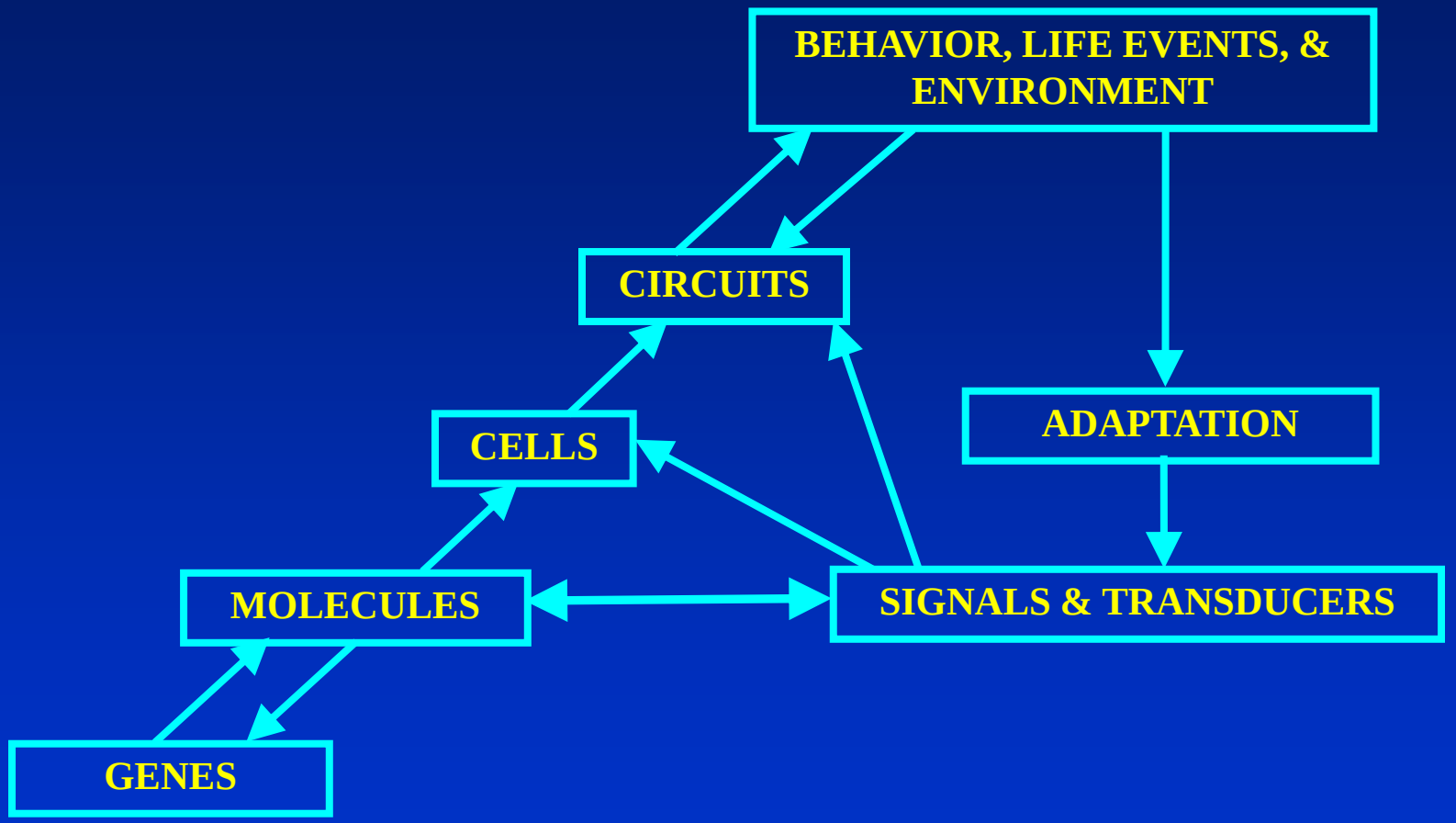
Merriman, Cameron (2007). Risk-taking: behind the warrior gene story. **NZ Medical Journal**

Complex Social Behaviors Integrate Multiple Gene Pathways: Neurogenomics

Economic Burden

• Violent Offenses:	$70 billion
• Stress-Related Affective Illness:	$125 billion
• Dementias	$100 billion
TOTAL	**$295 billion**

Aggression and Violence: A Systems Perspective

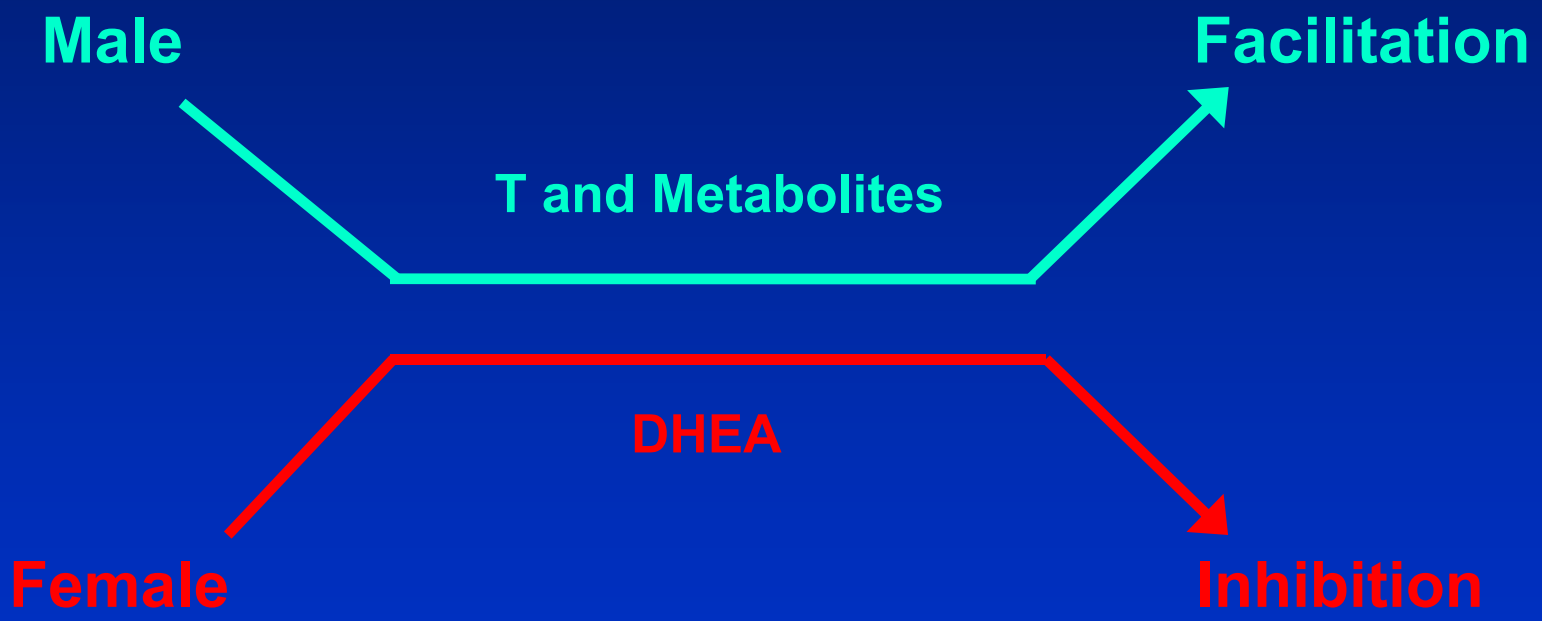


Definitions

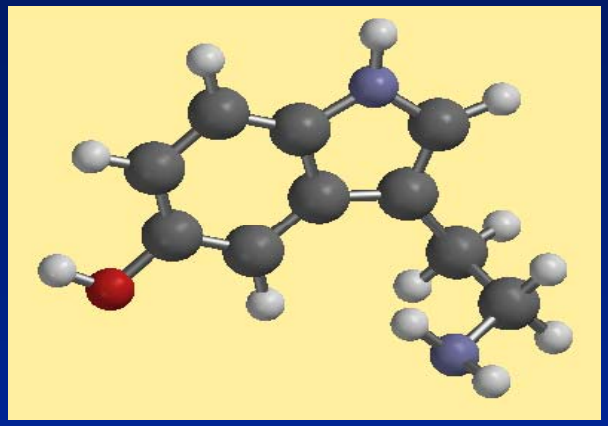
- **Conspecific Aggression**
  - Part of reproduction
  - Establishment of dominance status
  - Access to Resources

- **Violence/Inappropriate Aggression**
  - Intent to harm and cause injury
  - Assault, murder

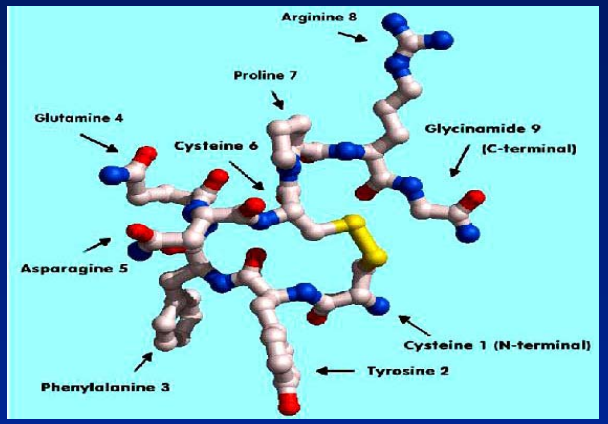
Sex Differences



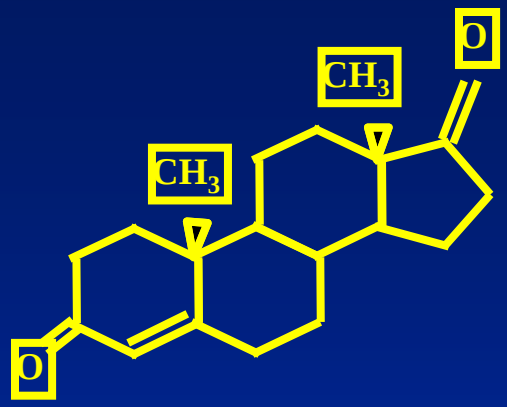
Target Systems



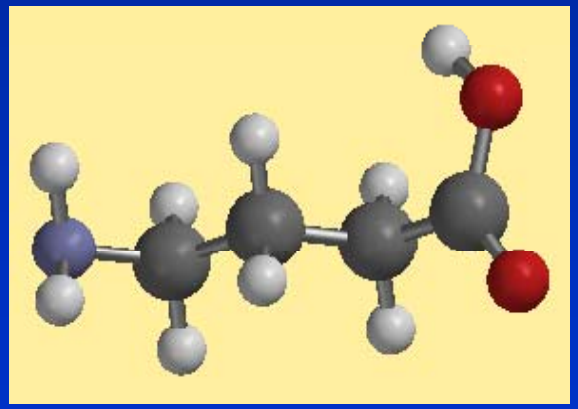
5-HT



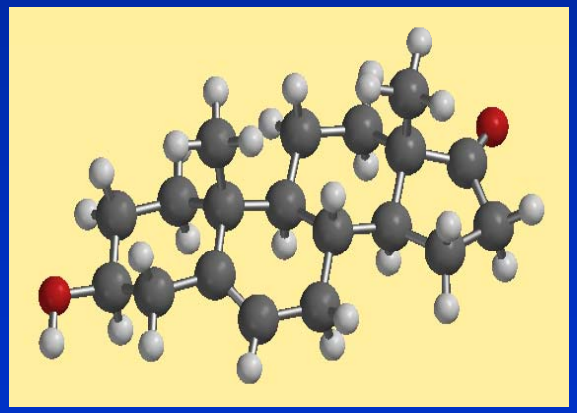
AVP



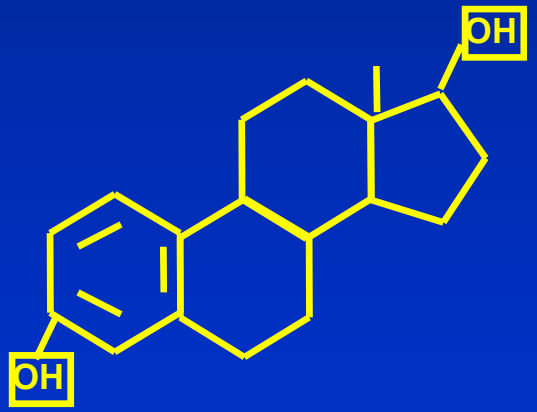
TESTOSTERONE



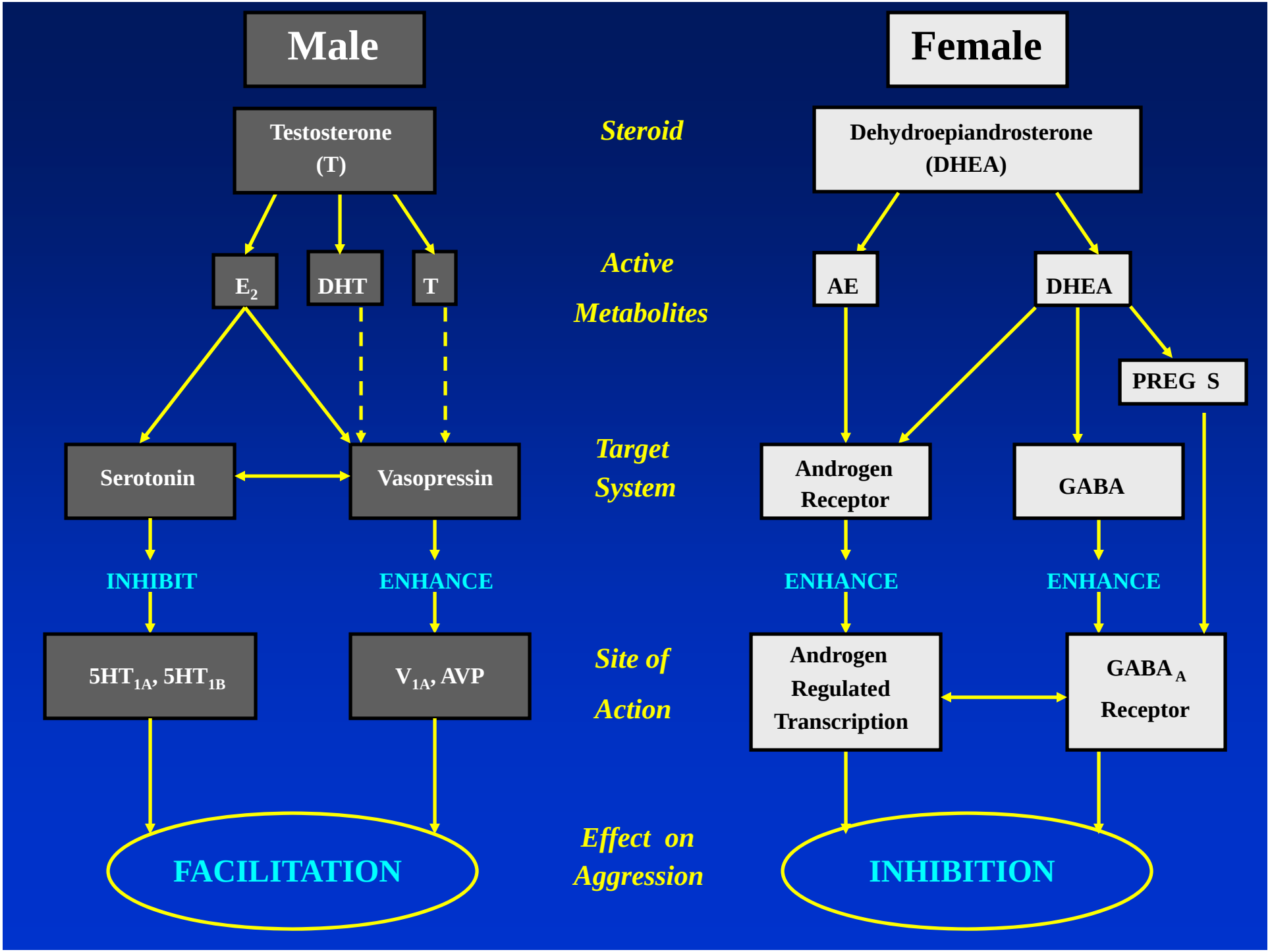
GABA



DHEA



ESTRADIOL


Male
Female
Testosterone (T)
Dehydroepiandrosterone (DHEA)
Steroid
E2
DHT
T
AE
DHEA
PREG S
Active Metabolites
Serotonin
Vasopressin
Androgen Receptor
GABA
Target System
INHIBIT
ENHANCE
ENHANCE
ENHANCE
5HT1A, 5HT1B
V1A, AVP
Androgen Regulated Transcription
GABA A Receptor
Site of Action
FACILITATION
INHIBITION
Effect on Aggression

MALES

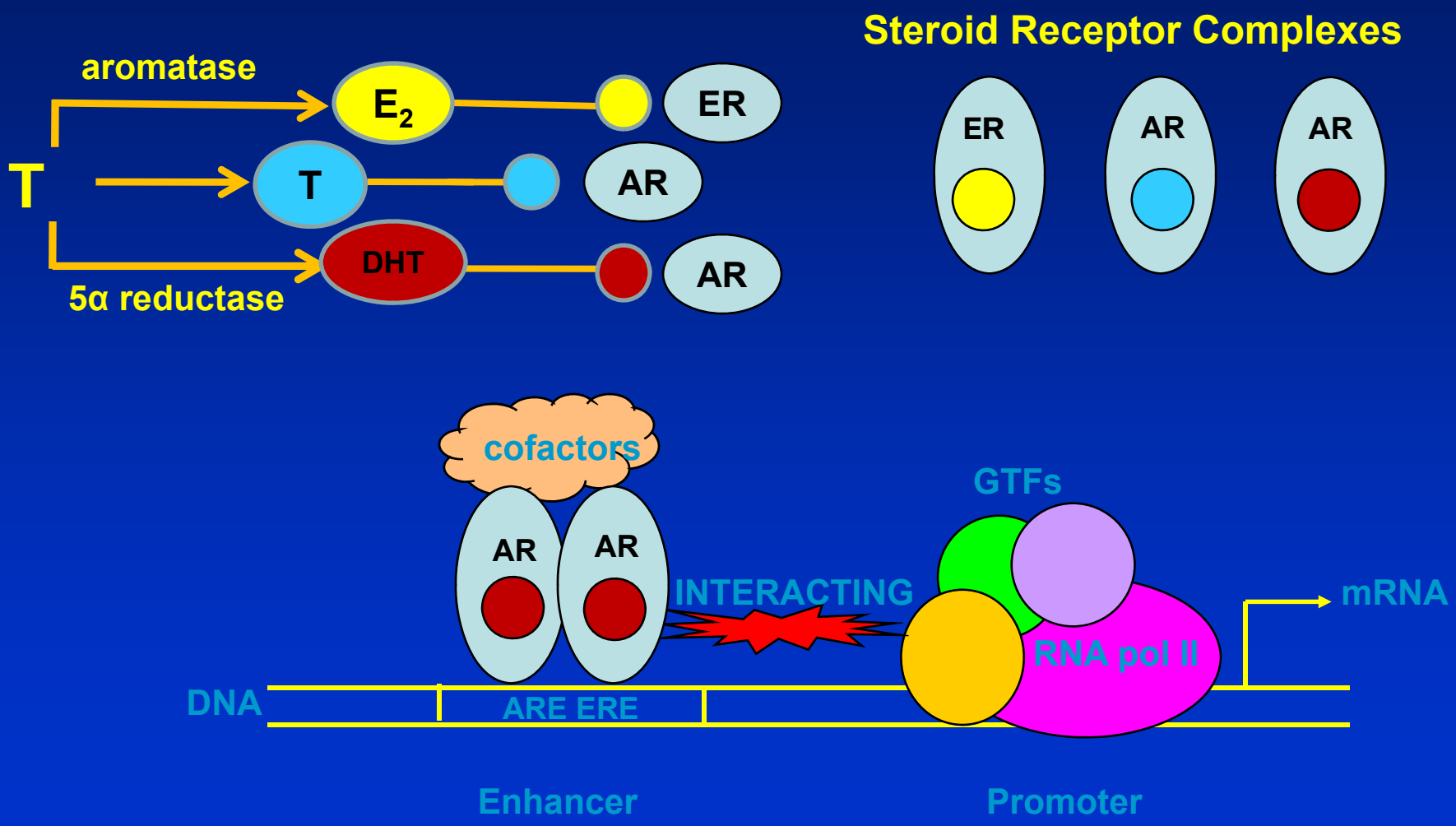
- Hormones
  - testosterone
  - estradiol
- Neurotransmitters
  - serotonin
  - vasopressin

Hormonal Hypotheses

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

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	+ +	+ +	+ +	+ +

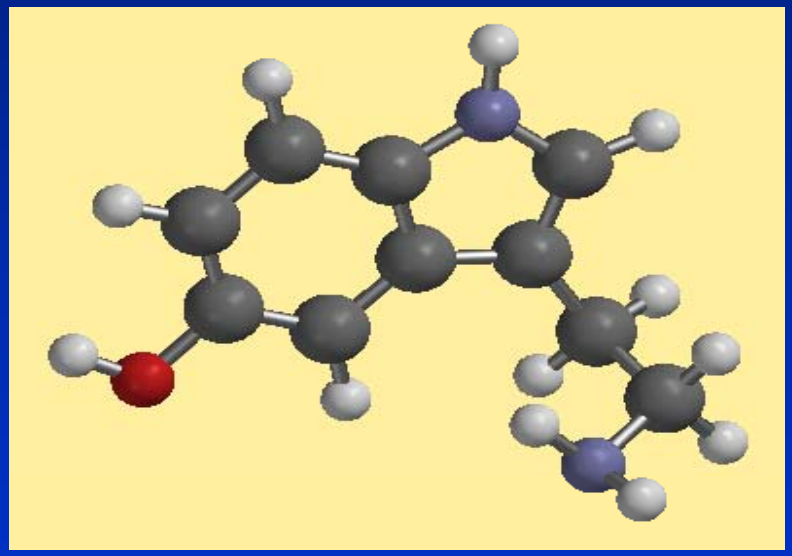
+ + high sensitivity + moderate sensitivity - insensitive

Biological Sciences

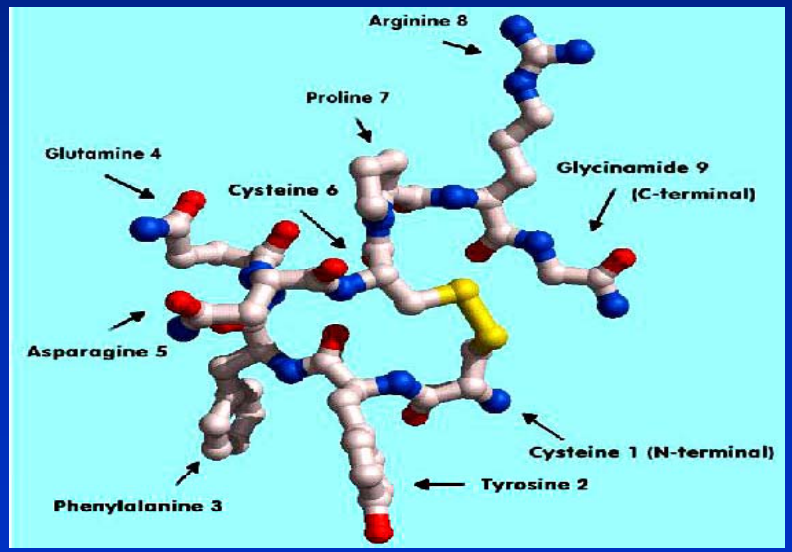
LEHIGH University

Androgenic Steroid Abuse: Roid Rage

Neurotransmitters

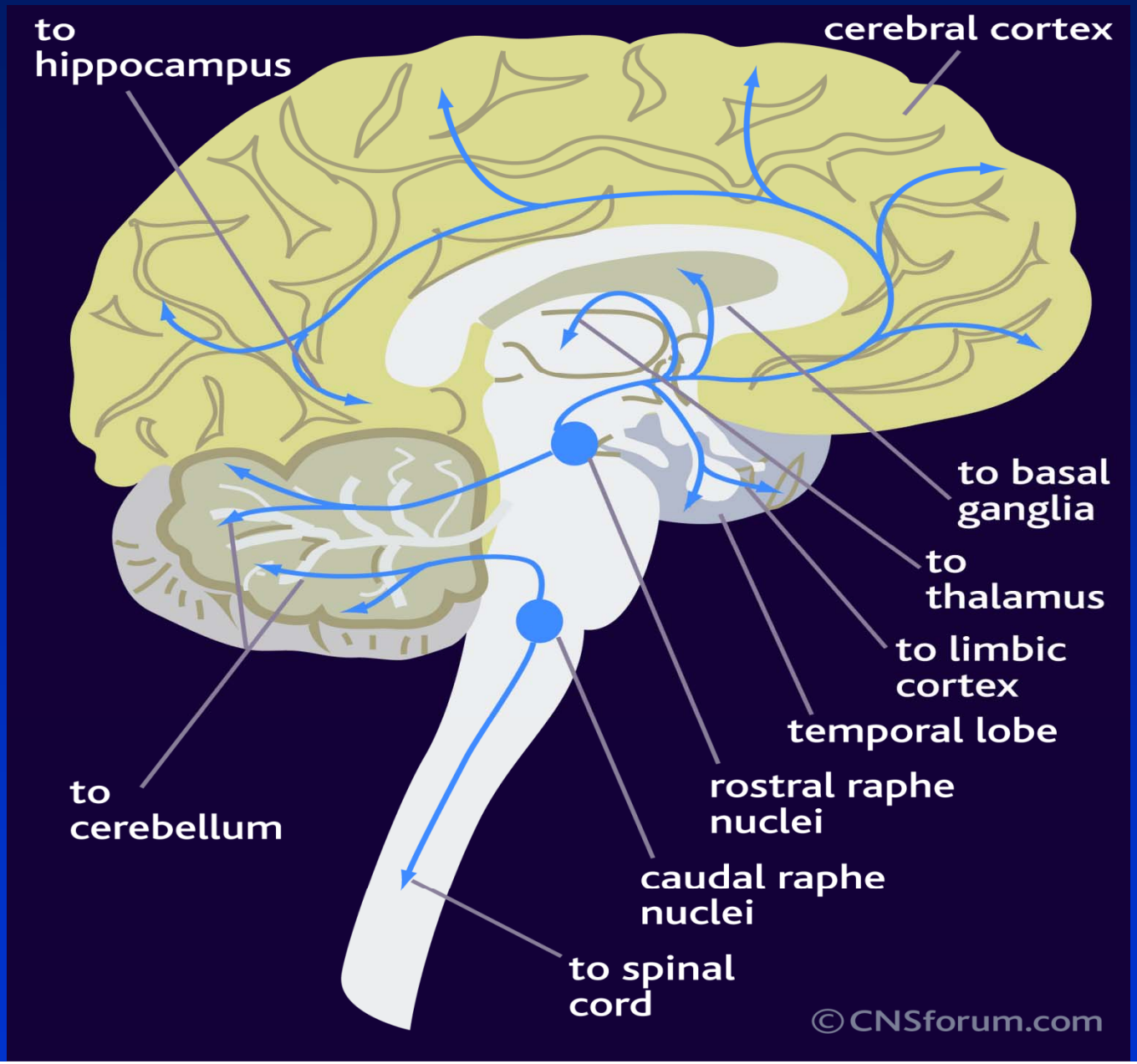


5HT



AVP

Serotonin System: Human Brain



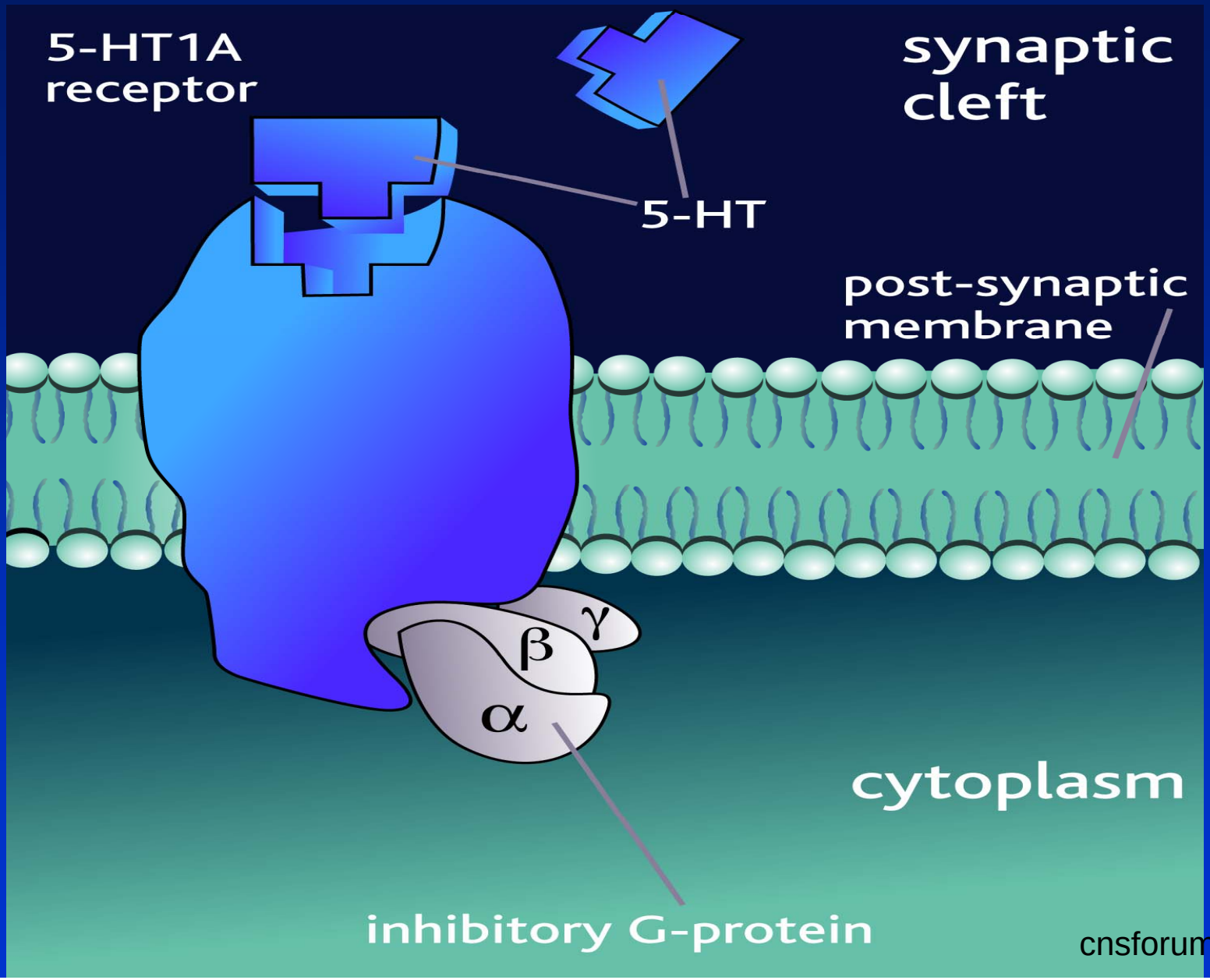
Serotonin and Aggression

Inhibitory

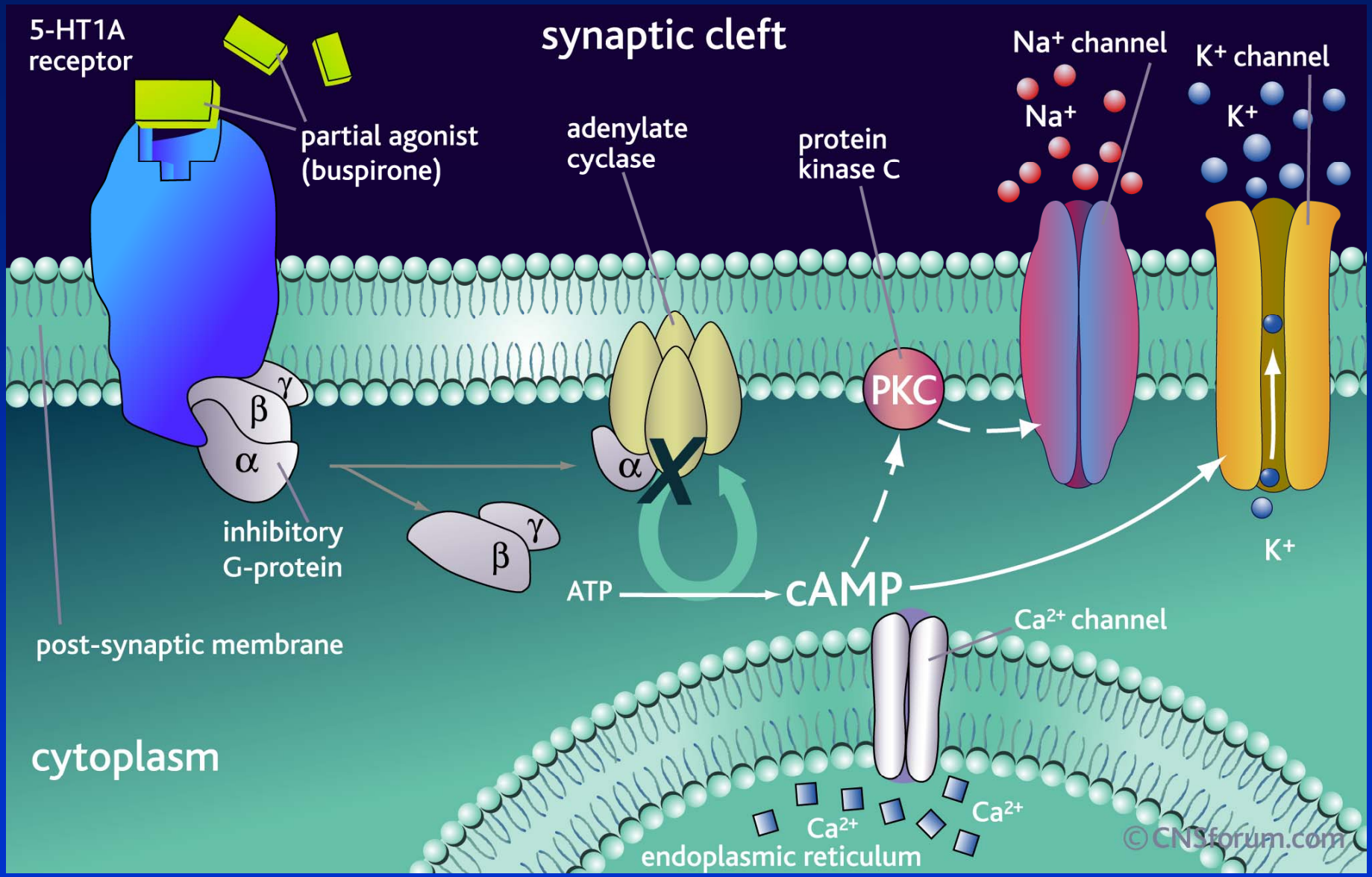
- **Pharmacology: 5HT1a and 5HT1b receptor**
- **Genetics: Knockout Mouse**
- **Human Impulsivity and Hostility**

THERE IS AN INVERSE RELATIONSHIP BETWEEN SEROTONIN FUNCTION AND AGGRESSION

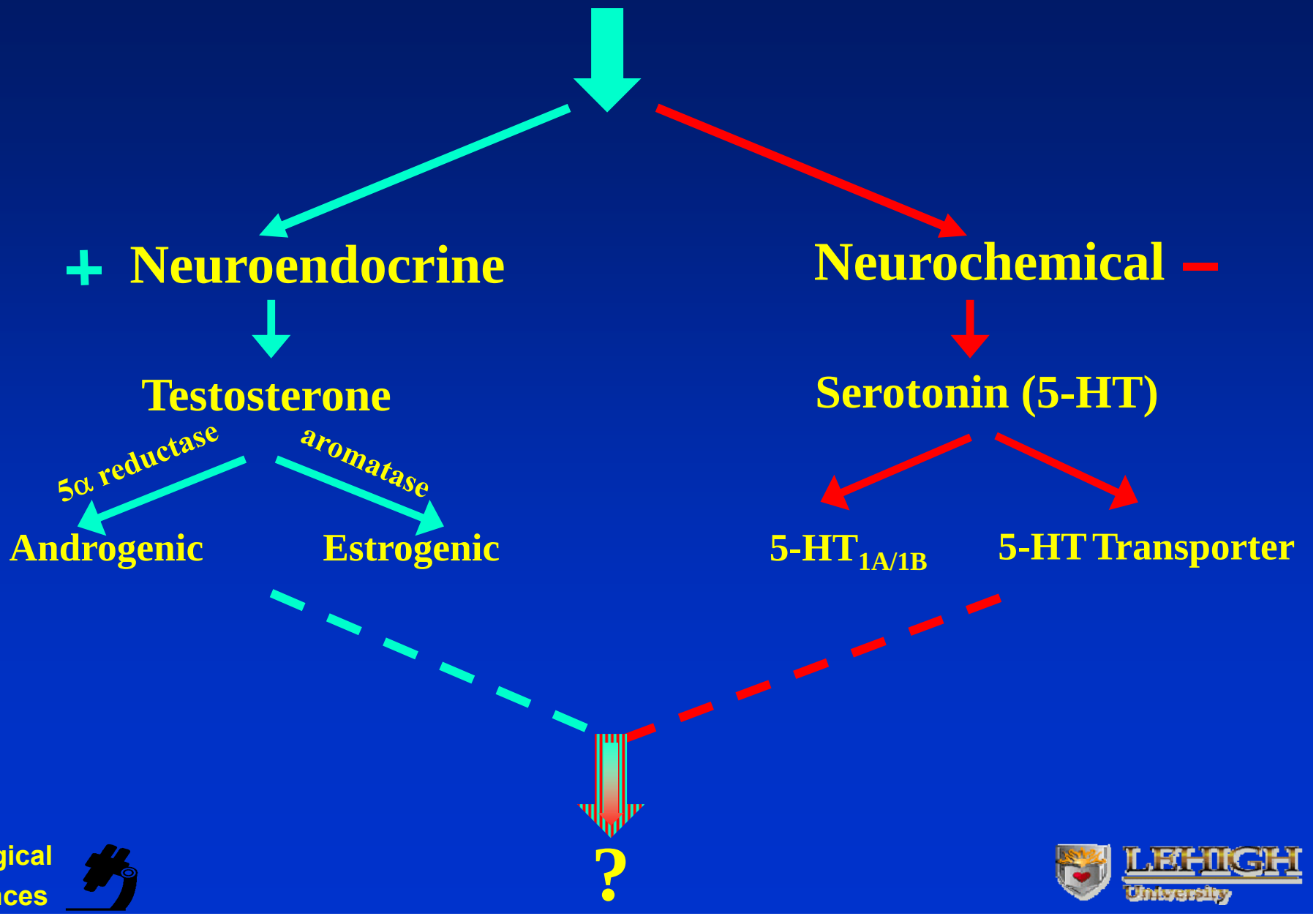
Serotonin 1a Receptor



Serotonin 1a Receptor: A GPCR Second Messenger System



Signal Integration: Testosterone and Serotonin



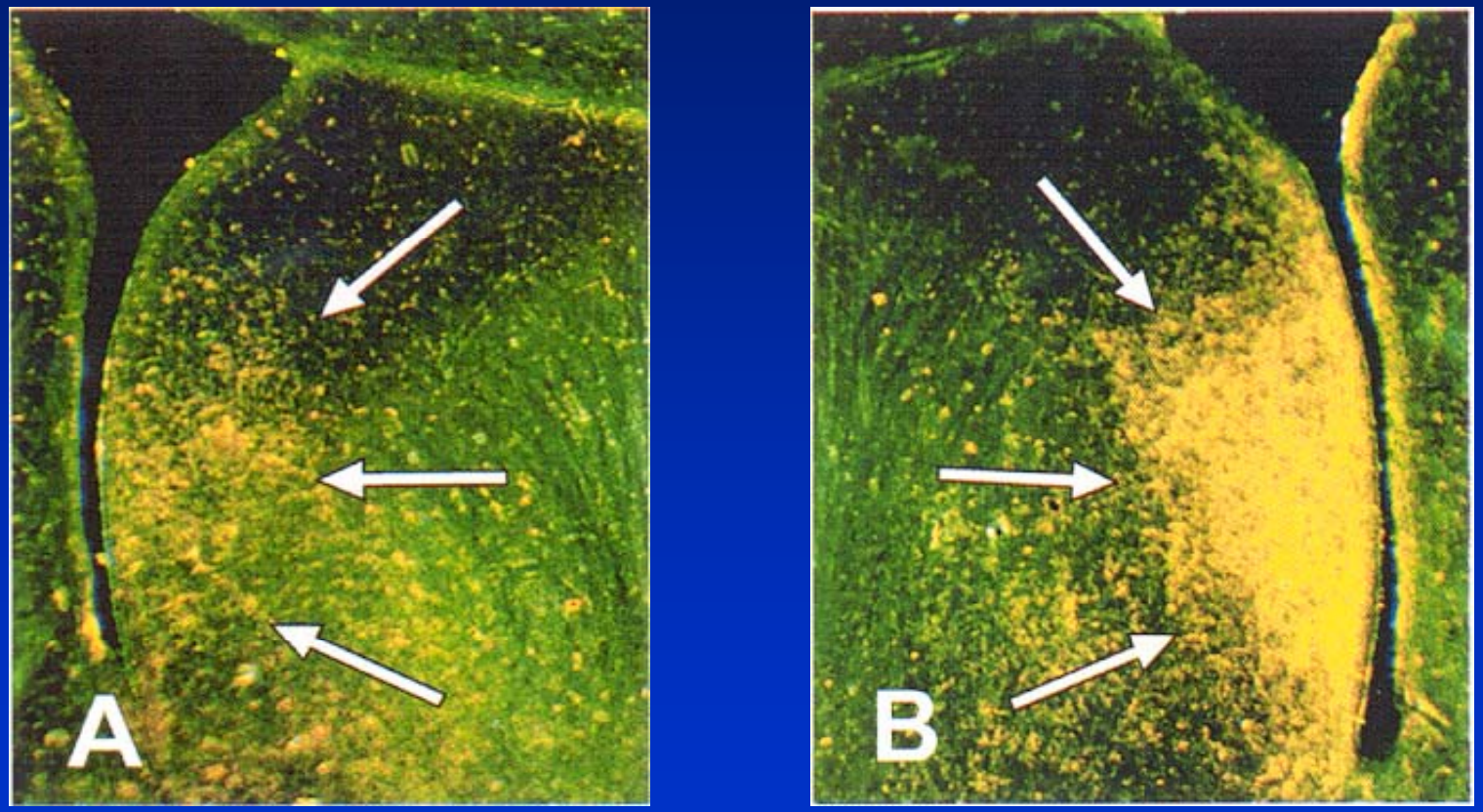
Summary: Males

- Multiple Steroidal Pathways
- Androgenic Modulation: Permissive
- Estrogenic Modulation: Restrictive

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

De Vries and Simerly, 2002

Vasopressin: Biological Diversity

Invertebrate & Vertebrate Physiology

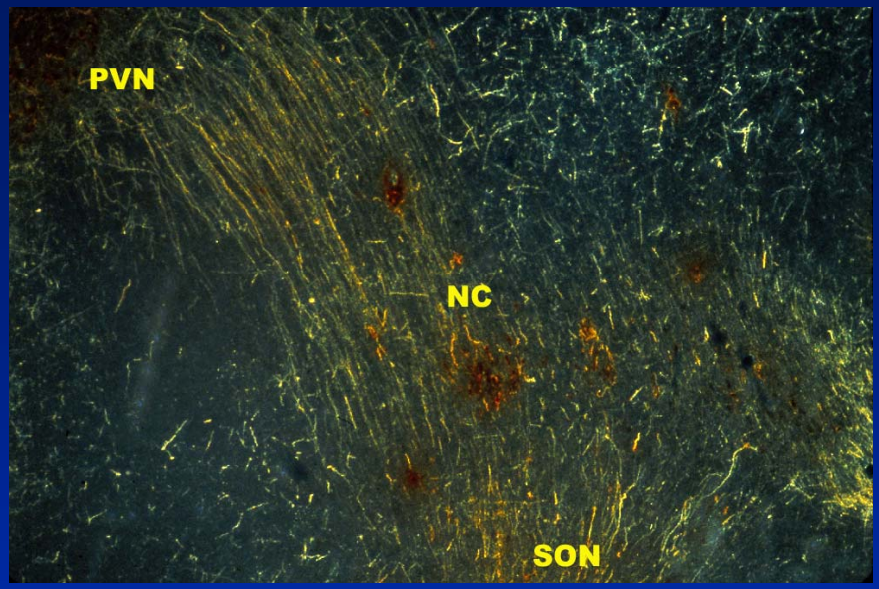
- fluid regulation
- carbohydrate metabolism
- thermoregulation
- reproductive function

Vertebrate Behavior

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

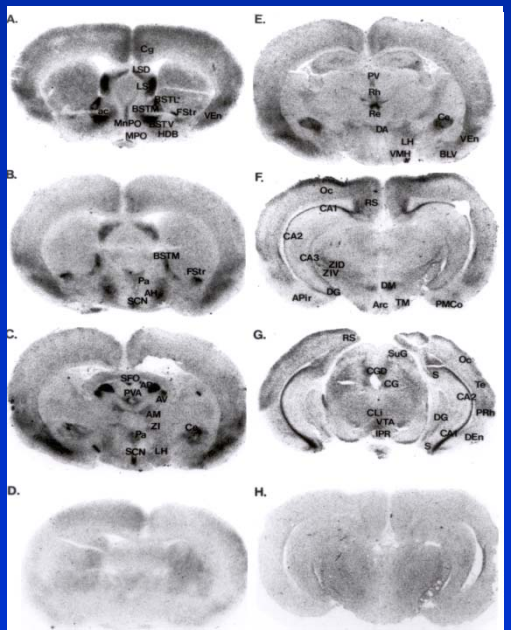
Brain Vasopressin System

- Vasopressin Neurons Localized to PVN, SON, Accessory Nuclei, BNST and Medial Amygdala

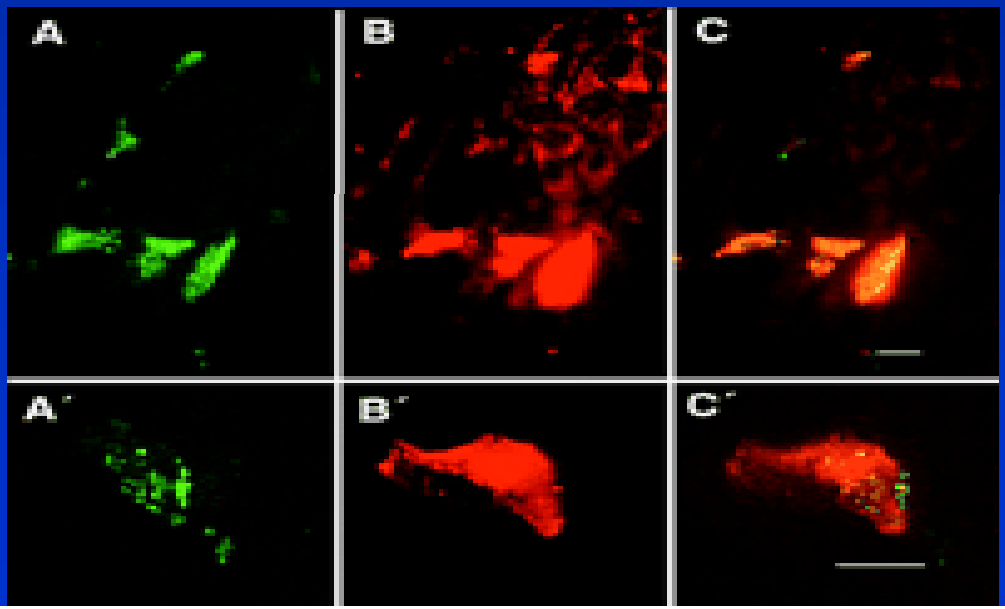


- V1a and V1b Receptors Mediate Behavioral Effects of AVP

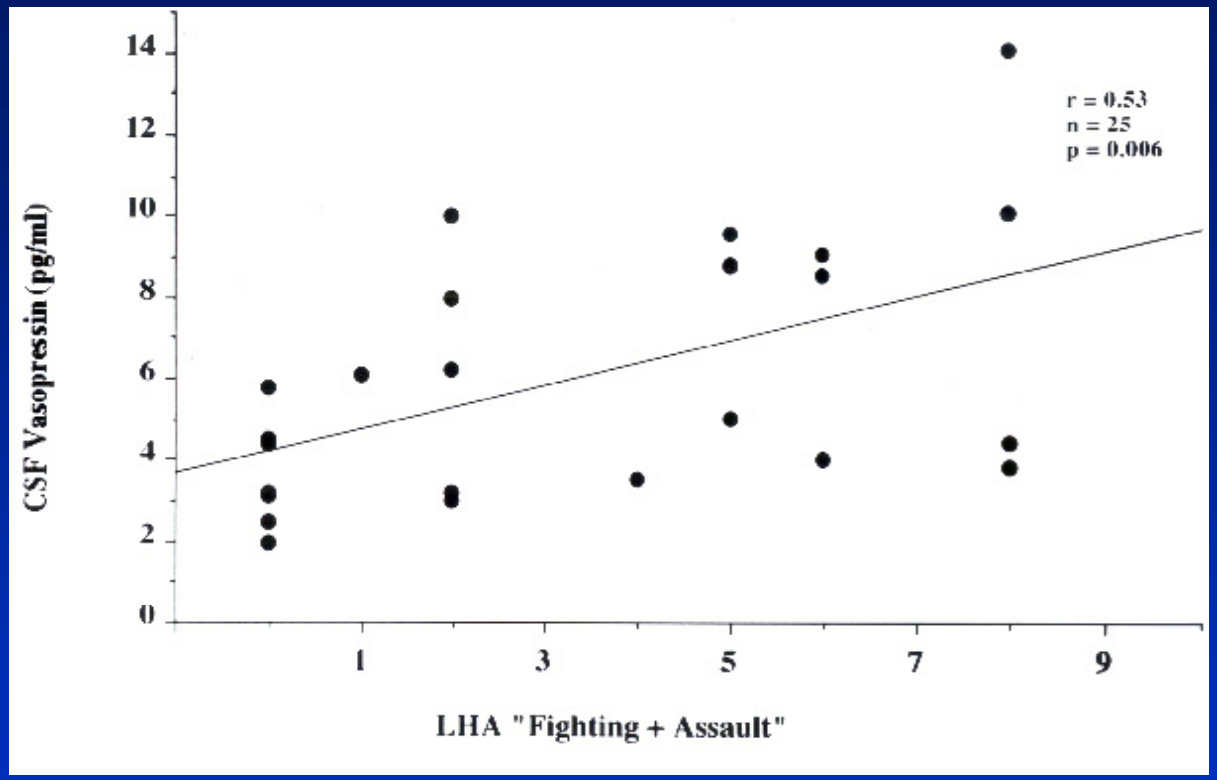
V1A Hamster



V1B in Rat Pituitary Corticotrophs



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

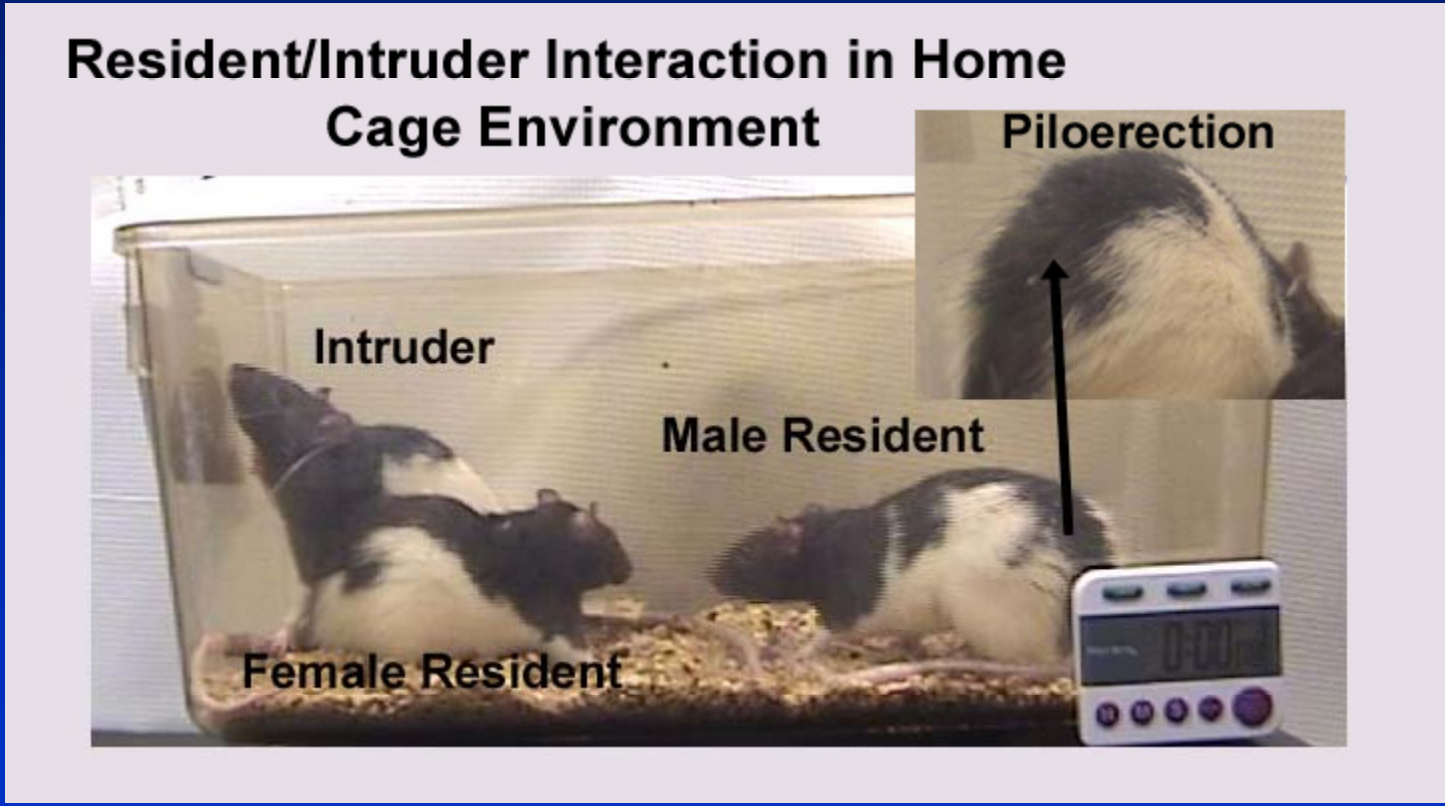


- Patients with history of “fighting & assault” show weak prolactin response to fenfluramine challenge.
- Prolactin levels are negatively correlated with CSF vasopressin levels.

Coccaro et al., 1998

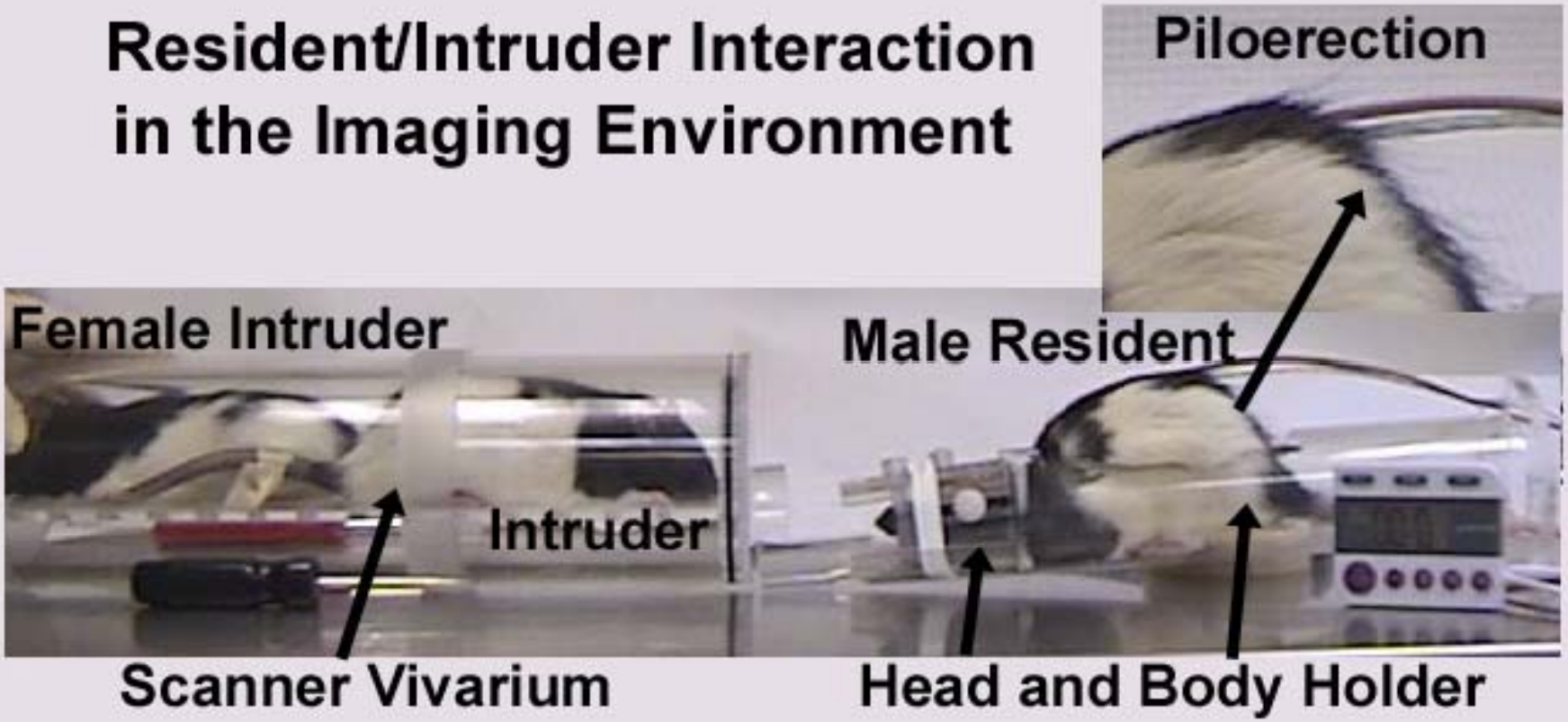
Imaging and Intervention

fMRI: Imaging Aggression in Awake Animals



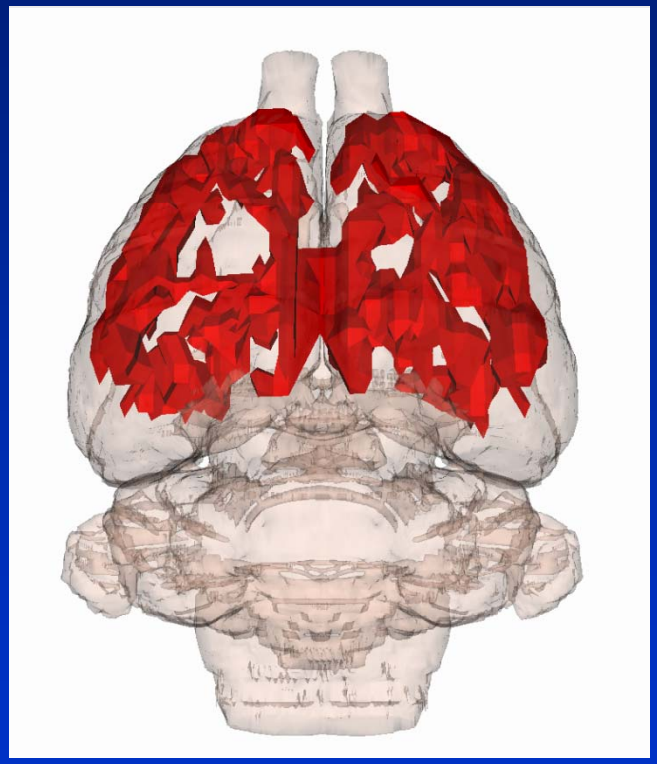
Piloerection is used as an indicator of autonomic activation

Social Arousal in the Imaging Environment

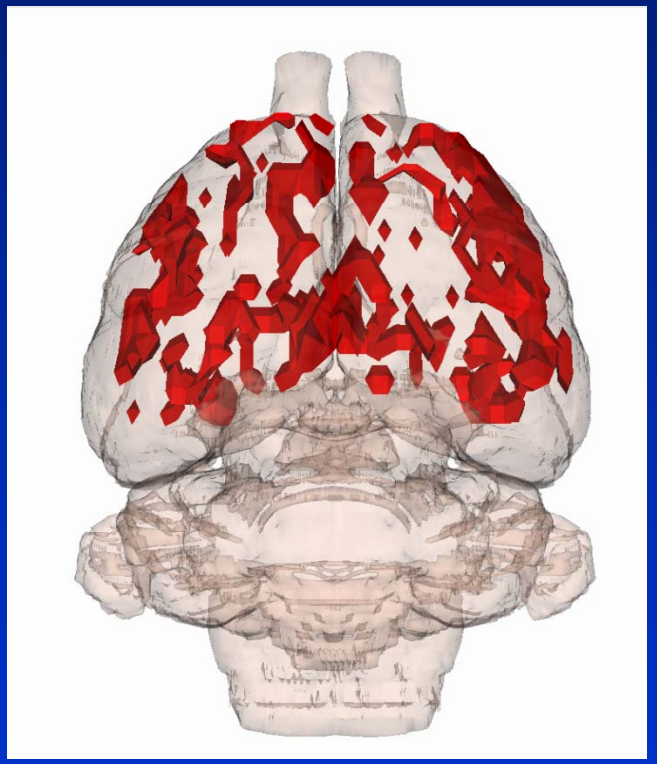


Vasopressin 1a Antagonism Blocks Aggression

Social Stress/Arousal in Response to an Intruder Male

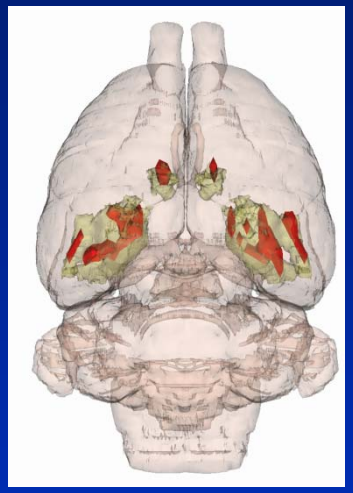
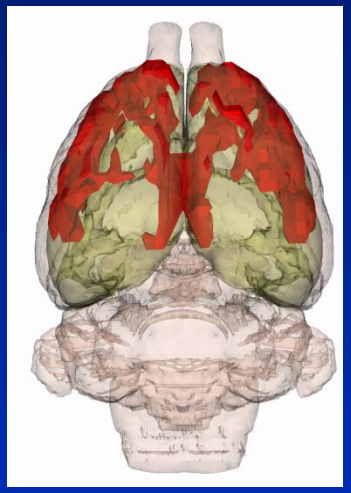
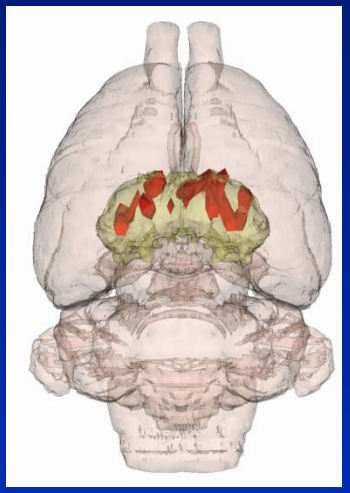
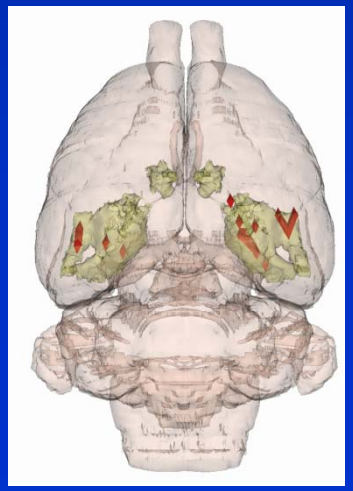
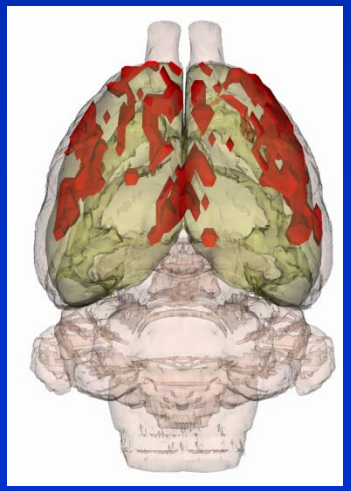
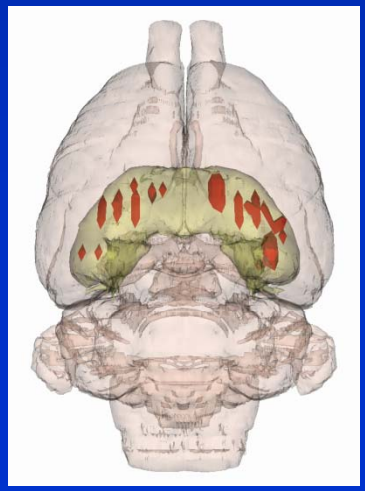
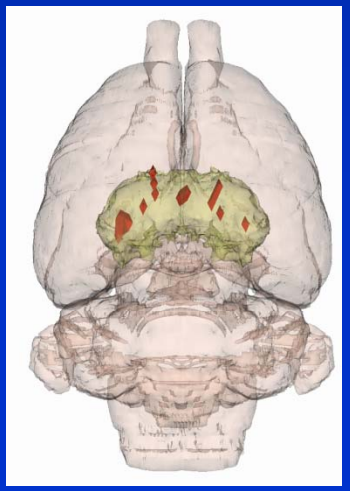


Activated Pathway



After Oral SRX251

Vasopressin 1a Antagonism Blocks Aggression

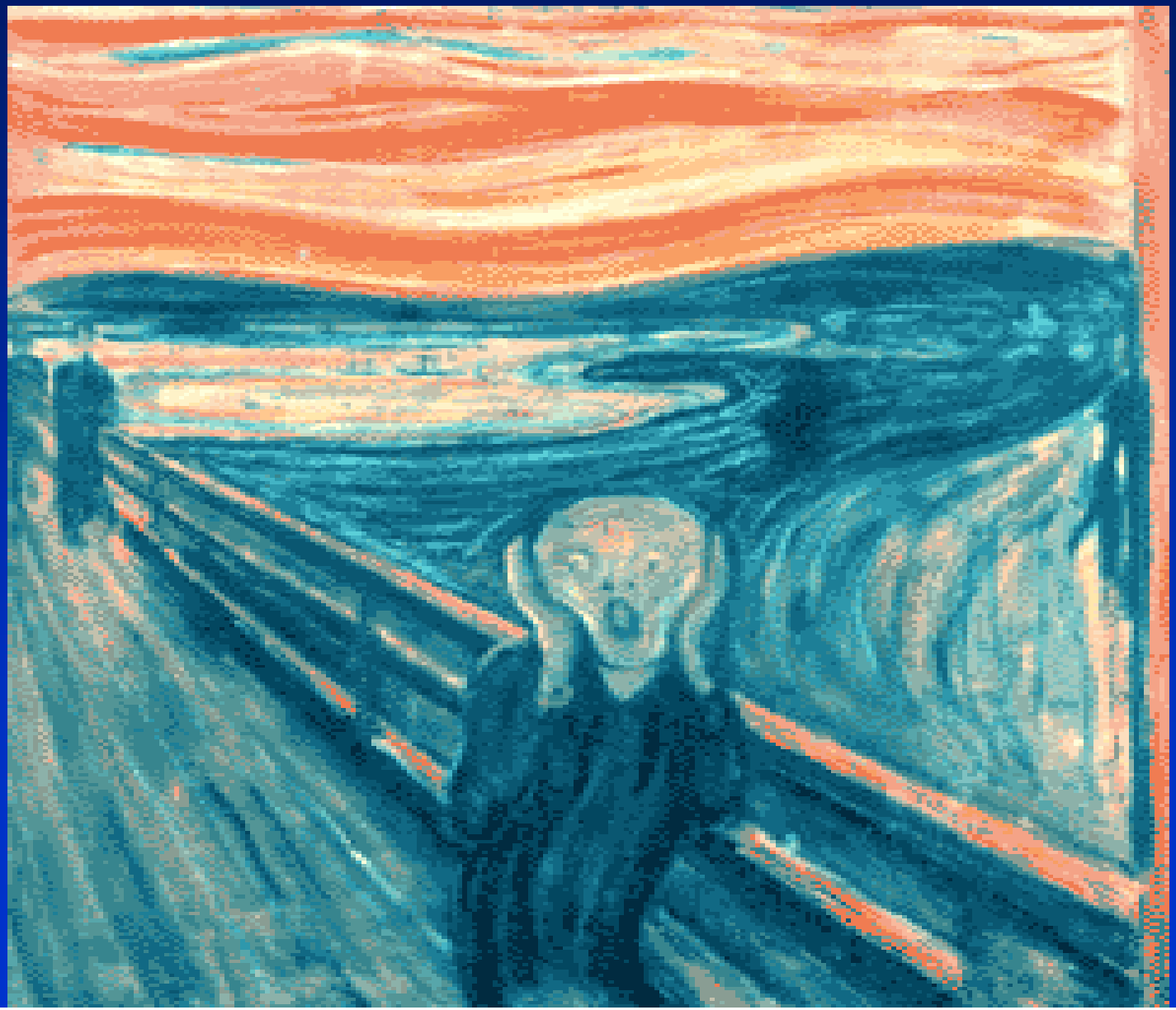
	Amygdala	Cortex	Hippocampus	Thalamus
Mate & Intruder				
SRX251 Treatment				

Summary

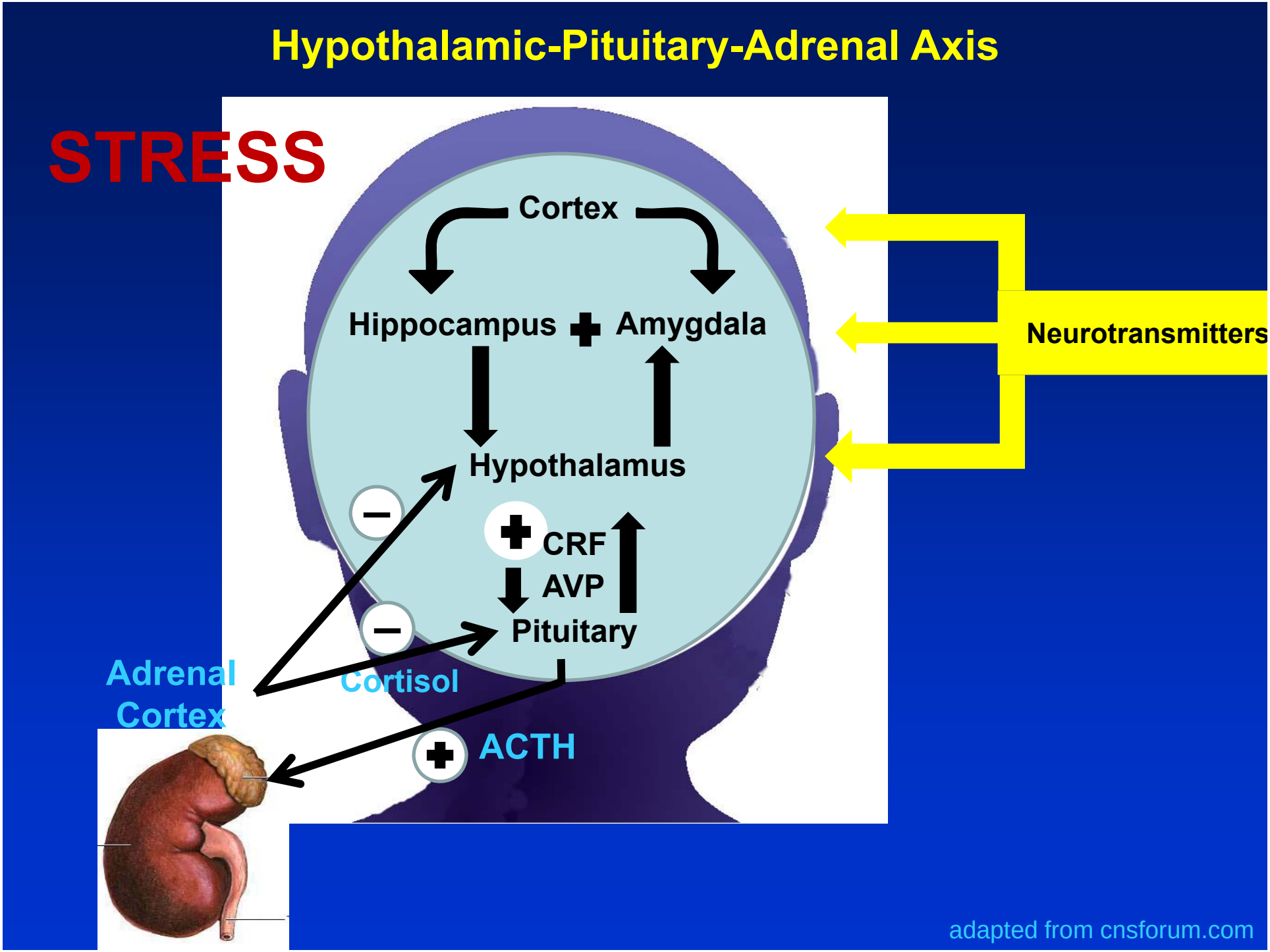
- Testosterone and its metabolites maintain AVP fibers and V1a receptor integrity

- 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

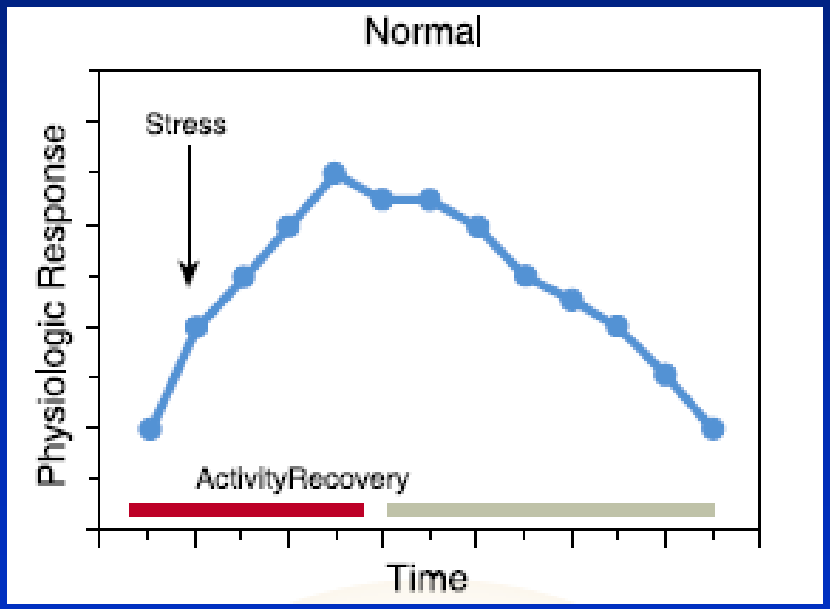


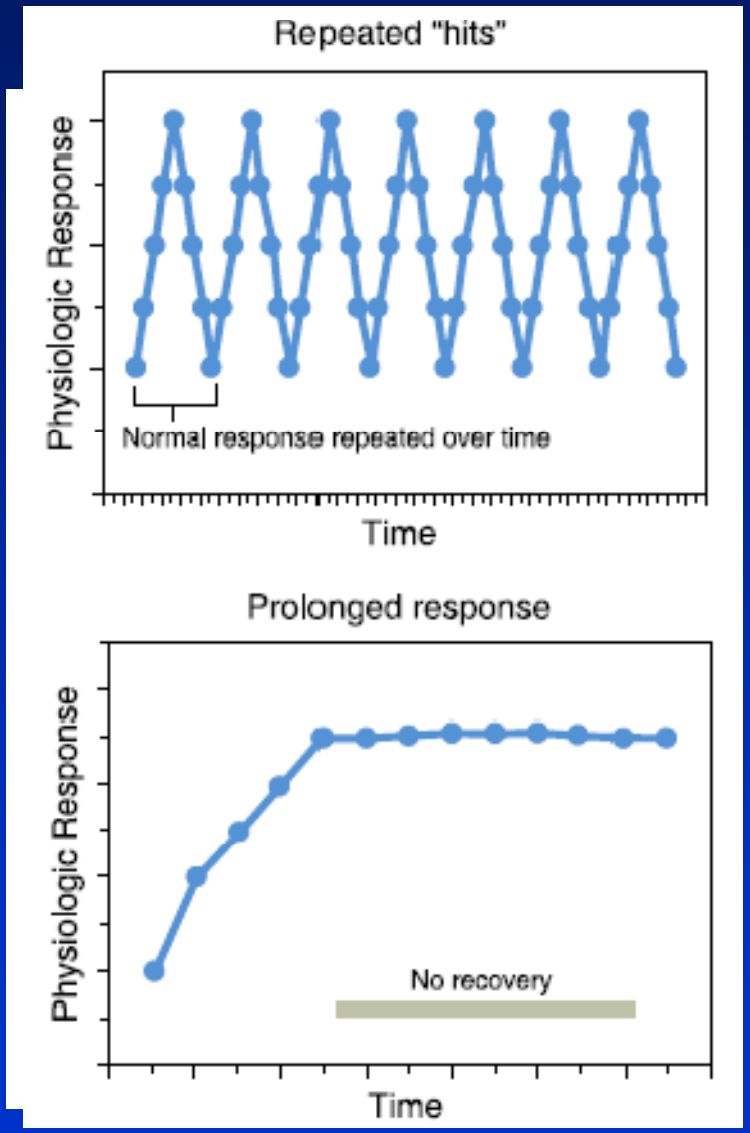
Hypothalamic-Pituitary-Adrenal Axis



adapted from cnsforum.com

Normal and Atypical Responses to Stress: Allostatic Load





McEwen (2007) Physiol. Rev.

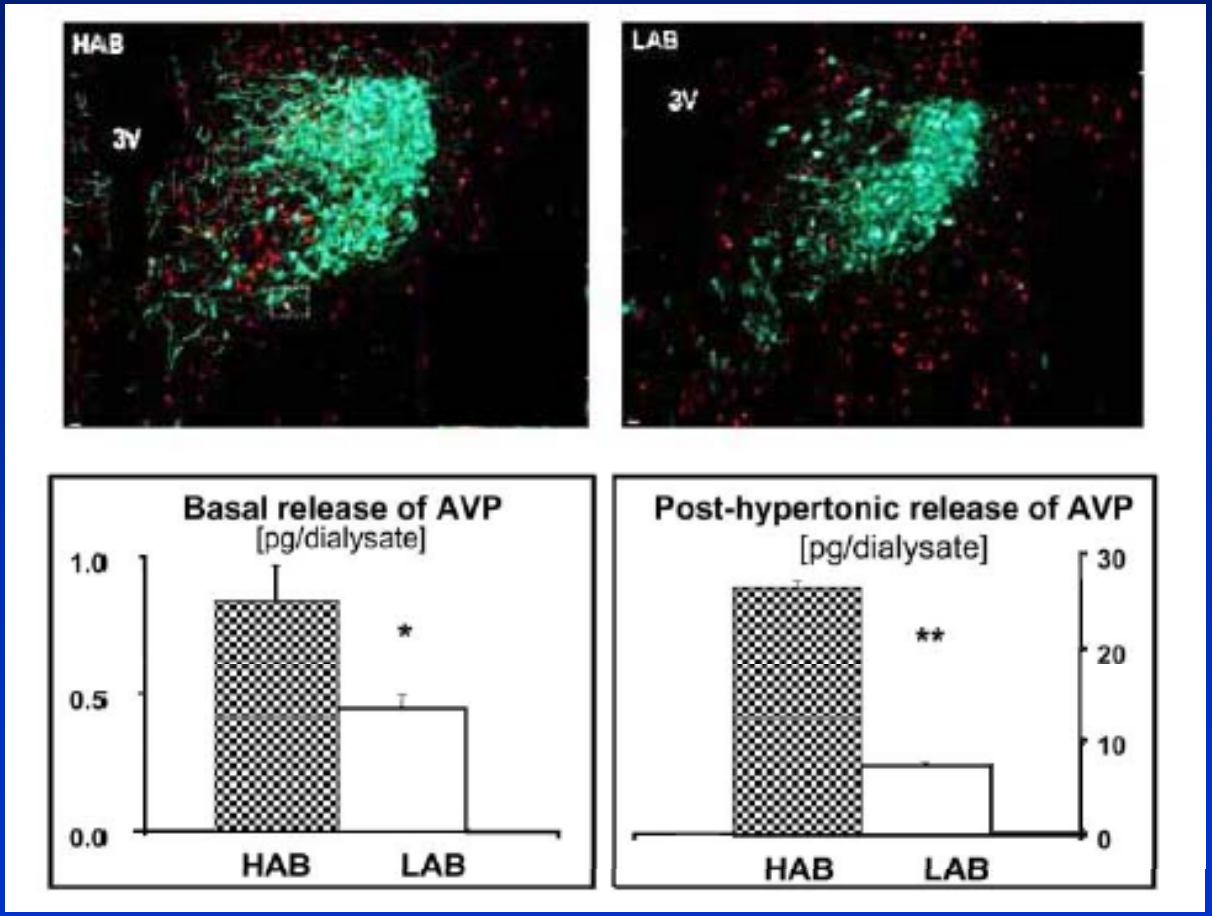
Social Subjugation/Chronic Defeat: Physiological Effects & Consequences

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

- Depression
- Anxiety
- Cardiovascular Disease
- Immune Compromise

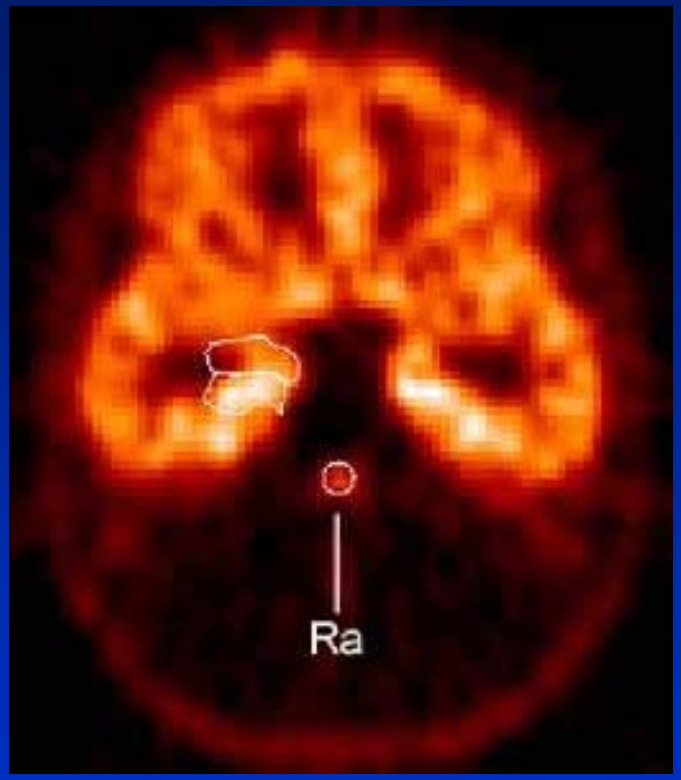
Vasopressin is Linked to Stress-related Disorders

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

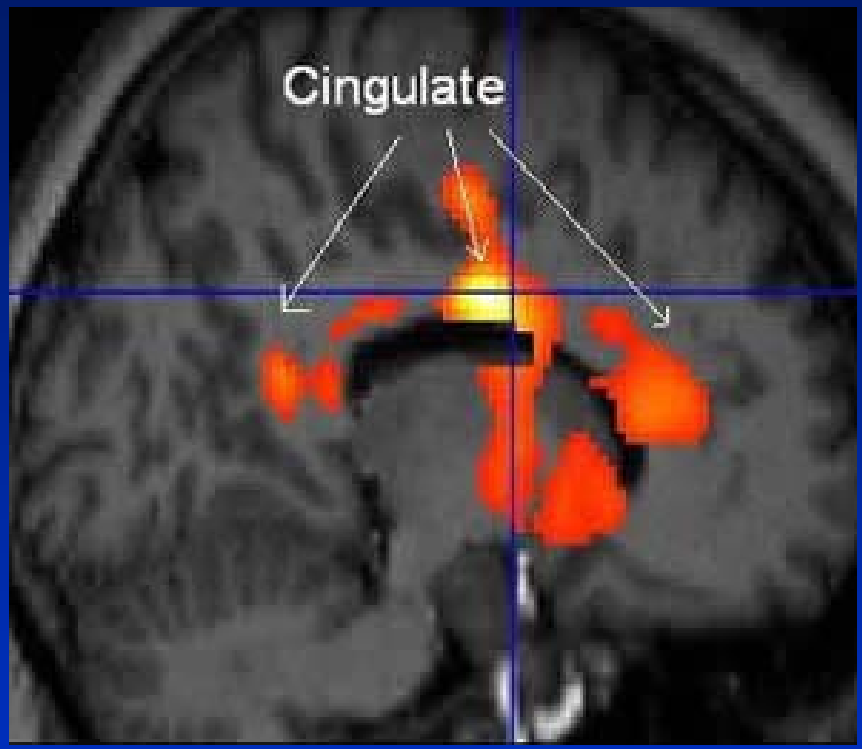


Synthesis, content, and release of AVP in PVN in HAB and LAB rats under basal and stress conditions

Panic Disorder and 5HT-1a 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.

Neumeister et al (2004) J Neurosci

Signal Processing in Depression

http://www.nimh.nih.gov/press/DeisserothDepressionCrossroadsBigger.mp4

Summary

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