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


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


*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

BEHAVIOR, LIFE EVENTS, & ENVIRONMENT

CIRCUITS

CELLS

MOLECULES

GENES

ADAPTATION

SIGNALS & TRANSDUCERS
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

Male

T and Metabolites

Female

Facilitation

DHEA

Inhibition
Target Systems

5-HT

AVP

TESTOSTERONE

GABA

DHEA

ESTRADIOL
Testosterone Steroid

Dehydroepiandrosterone (DHEA)

Male

Testosterone (T)

E₂

DHT

T

Serotonin

Vasopressin

INHIBIT

ENHANCE

5HT₁₅, 5HT₁₆

V₁₅, AVP

FACILITATION

Steroid

Active

Metabolites

Target

System

Site of

Action

Effect on

Aggression

Female

Androgen Receptor

GABA

ENHANCE

ENHANCE

Androgen Regulated Transcription

GABAₐ Receptor

PREG S

INHIBITION
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

Diagram:
- T (Testosterone) metabolized by aromatase to E2 (Estrogen), which binds to ER (Estrogen Receptor) and AR (Androgen Receptor).
- T is converted to DHT (Dihydrotestosterone) by 5α reductase, also binding to AR.
- Steroid Receptor Complexes:
  - ER
  - AR

- mRNA is transcribed from DNA via RNA polymerase II (RNA pol II), interacting with cofactors.
- Enhancer and Promoter regions on DNA interact with GTFs (General Transcription Factors) for transcription.
# Neuroendocrine Regulatory Systems for Intermale Aggression

<table>
<thead>
<tr>
<th>Androgen Sensitive</th>
<th>Estrogen Sensitive</th>
<th>Combined or Synergistic</th>
<th>Direct</th>
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<tbody>
<tr>
<td>Male</td>
<td>+ +</td>
<td>+ +</td>
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<tr>
<td>+ + high sensitivity</td>
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</tbody>
</table>

- **Male**
  - + + high sensitivity
  - + moderate sensitivity
  - - insensitive
Androgenic Steroid Abuse: Roid Rage

www.byjamesraia.com

phenomenaonbreak.wordpress.com
Neurotransmitters

5HT

AVP
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

5-HT1A receptor

5-HT

synaptic cleft

post-synaptic membrane

cytoplasm

inhibitory G-protein
Signal Integration: Testosterone and Serotonin

+ Neuroendocrine

- Neurochemical

Testosterone

5α-reductase
Androgenic

5-HT₁A/₁B

5-HT Transporter

- Estrogenic

5-HT Transporter

- Serotonin (5-HT)

Biological Sciences
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
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
Piloerection is used as an indicator of autonomic activation.
Social Arousal in the Imaging Environment

Resident/Intruder Interaction in the Imaging Environment

Female Intruder
Intruder
Scanner Vivarium

Male Resident
Head and Body Holder

Piloerection
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

STRESS

- Cortex
- Hypothalamus
- Hippocampus
- Amygdala
- Adrenal Cortex
- Cortisol
- ACTH
- CRF
- AVP
- Pituitary

Neurotransmitters

adapted from cnsforum.com
Normal and Atypical Responses to Stress: Allostatic Load

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


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.

Signal Processing in Depression

Summary

• Chronic subjugation disrupts conspecific aggression
• 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