Stress-related CNS Disorders: Neurobiology, Behavior, & Translational Models

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Outline

A. Common Indications

B. Basic Neurobiology
   1. Emotional Circuitry: Key Components
   2. The Hypothalamic Pituitary Adrenal (HPA) Axis

C. Preclinical Models & Translational Medicine
Stress-related CNS Disorders

- **Major Depression**¹
  - 15 million in US & growing globally
  - Current standard of care: SRIs/NRIs, 60% of patients do not respond

- **Intermittent Explosive Disorder**²
  - 12 million in US
  - Current standard of care: no approved treatment, off-label use of SSRIs

- **Impulse Control/Anger Disorders**
  - Core component of borderline personality, antisocial personality, and conduct disorders
    - 12 million in US
  - Common co-morbidity impacting therapeutic response in PTSD, ADHD, & psychoses
  - Current standard of care: no approved treatment

- **Post-Traumatic Stress Disorder (PTSD)**³
  - 8 million in US, a priority indication for military medicine
  - Major Depression, Intermittent Explosive Disorder, Impulse Control Disorders are co-morbid
  - Current standard of care: repurposed SSRIs

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¹ Mathew & Charney (2009); NIMH ² Coccaro (2002); Kessler et al. (2006) ³ NIMH; USAMRMC
Stress-related Disorders: Disturbed Affect
B. Basic Neurobiology & Physiology
The Emotional Brain: Papez Circuit

Papez Circuit

Cingulate cortex
Anterior n
Mammillary body
Fornix
Hippocampus

Cortical Circuit of Papez

prelimbic ctx
2nd motor ctx
supraorbital ctx
retrosplenial ctx
insula ctx
primary somatosensory ctx
entorhinal ctx
mammillary bodies
anterior thalamus

Amygdala

bed nucleus stria terminalis
central n.
lareral n.
cortical n.
medial n.
basal n.
posterior n.

Hippocampus
dentate
CA1
subiculum
CA3

Rat
The Emotional Brain

McLean, 1949
Hypothalamic-Pituitary-Adrenal Axis
1. The Hypothalamic-Pituitary-Adrenal Axis

Key Considerations

- **Regulatory Peptides**
  - CRF
  - AVP

- **Feedback Regulation**
  - Glucocorticoids

- **Rhythm Disturbance**
  - Sleep
  - Cardiovascular
  - Core Temperature
  - Activity
Anatomical Circuits: Medial Prefrontal Network & Amygdala

Price & Drevets (2010)
C. Preclinical Models & Translational Medicine: Vasopressin
Arginine Vasopressin: Receptor Subtypes & Localization

Central Nervous System: V1a and V1b

- HPA axis regulation and behavioral effects of vasopressin mediated by activation of V1a and/or V1b receptors
- V1a is the dominant CNS subtype
- V1a shows extensive limbic system and cortical distribution

Anterior Pituitary: V1b

- Response to ACTH and HPA axis regulation

Periphery: V1a and V2

- V1a: smooth muscle and blood vessel wall
- V2: kidney (antidiuretic hormone)
# Vasopressin Antagonists: Clinical Indications

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<thead>
<tr>
<th>V1a Antagonist</th>
<th>V2 Antagonist</th>
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<td>Congestive Heart Failure</td>
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<td>ACTH-secreting tumors</td>
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<td>Motion sickness</td>
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Elevated Vasopressin is Linked to Stress-related Disorders: Rodent Models

AVP in the paraventricular nucleus (PVN) flanking the 3rd ventricle (3V) in HAB (high depression/anxiety) and LAB (low depression/anxiety) mice.

Behavioral phenotype of the High (HAB), Low (LAB), and Normal (N) depression/anxiety mice in representative tests.

Elevated Plus Maze

Forced Swim Test

Bunck et al. (2009)
**Method.** A 10-day subjugation paradigm that leads to diminished social interaction behavior recently was described by Berton et al (2006). Treatment regimen with fluoxetine, a gold-standard antidepressant, reversed deficits while chlordiazepoxide (CDP), a well-known anxiolytic, had no effect. These observations are consistent with the subjugation/social interaction model as a rapid behavioral screen for potential antidepressants. **Results.** Vasopressin Receptor Antagonist treatment led to a significant increase in distance in the interaction zone and the time measure also was in the expected direction. In contrast, chlordiazepoxide had no significant effect.
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)


Biological Sciences
Altered Cerebral Blood Flow in Major Depressive Disorder

Price & Drevets (2010)
PTSD: A Complex Disorder with Frequent Co-morbidities

- **Major Symptoms**
  - Hyperarousal to Traumatic Memory
  - Emotional Dysregulation

- **Common co-Morbidities**
  - Major Depression
  - Anxiety Disorders
  - Impulsivity/Violent Behavior
  - Substance Abuse
Predatory Conditioned Fear – A Model of PTSD

sable ferret

rat

Imaging Protocol

ferret

5 min stimulus

5 min control

Physiology

ferret

heart rate

blood pressure

respiratory rate

40 sec
Emotional Memory Disturbance: The Memory of Fear is Worse Than Fear Itself

Method: Male rats were exposed to a ferret (a natural predator and an unconditioned stimulus, UCS) paired with sucrose (conditioned stimulus, CS). Fourteen days later, the males were exposed to sucrose alone. Result: BOLD activation showed hyperarousal in response to sucrose alone in regions linked to fear and memory retrieval.
Vasopressin Receptor Blockade is Effective in a Conditioned Fear PTSD Model

- V1a receptor block significantly reduced hyperarousal in brain regions mediating fear & memory two weeks after traumatic fear conditioning
- Normal fear responses & arousal patterns were unaffected
Plasma AVP is Elevated in Combat Veterans with PTSD

Plasma AVP in veterans with PTSD (far left) and controls that were 1) veterans that experienced trauma but not PTSD (TC; center column) or healthy civilians (right)

de Kloet et al (2008)
Intermittent Explosive Disorder/Anger Disorders

- Repeated episodes of aggression toward self and/or others
- Property Destruction
- Explosive Outbursts & Temper Tantrums
- Compromised Relationships
- Remorse, regret, and guilt
Vasopressin Antagonists Block Stress, Arousal, & Fear in a Rat Model: Composite View

- Stress/Arousal Circuitry activity is attenuated to intruder stimulus
- Sexual motivation, performance, and activity are unaffected
Vasopressin Blockade: Neuroimaging in Major Brain Regions Linked to Stress-related Disorders

- AVP Blockade attenuates arousal, stress, fear, and aggressive motivation
- Sexual motivation and performance remain intact

From Ferris et al. (2008)
Correlation between Aggression Against Persons (the fighting and assault items) scores on the Life History of Aggression (LHA) assessment and cerebrospinal fluid (CSF) arginine vasopression (AVP) concentrations in 26 individuals who met the DSM-IV criteria for personality disorder.

Coccaro et al (1997)
Vasopressin & Negative Stimuli Processing: Prefrontal Cortex-Amygdala Connectivity

Zink et al (2010)
Summary: Peptides & Stress-related Disorders

- CNS AVP receptors are implicated in stress-related disorders through preclinical models & human results

- Human studies suggest the involvement of the vasopressin system

- Disease-specific circuitry remains to be characterized

- Social Neurobiology can potentially identify new pathways for intervention
Mood Disorders: Medial Prefrontal Network & Amygdala

Price & Drevets (2010)
Thank you for your time and attention