Stress-related CNS Disorders: From Bench to Bedside

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Outline

A. Common Indications

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

C. Preclinical Models & Translational Medicine

D. Drug Development
The Emotional Brain: Papez Circuit
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

\(^1\) Mathew & Charney (2009); NIMH \(^2\) Coccaro (2002); Kessler et al. (2006) \(^3\) NIMH; USAMRMC
B. Basic Neurobiology
Hypothalamic-Pituitary-Adrenal Axis

Key Considerations

- **Regulatory Peptides**
  - CRF
  - AVP

- **Feedback Regulation**
  - Glucocorticoids

Biological Sciences
Fear Circuits: Core Components

- Hippocampus and Amygdala
- Anterior & Rostral Cingulate Cortex
- Insular Cortex

Edvard Munch, 1893
Shin & Liberzon (2010)
B. Preclinical Models & Translational Medicine: Peptide Receptors as Drug Targets
Vasopressin is Linked to Stress-related Disorders


Synthesis, content, and release of AVP in PVN in high depression/anxiety (HAB) and low depression/anxiety (LAB) rats under basal and stressed conditions
## Vasopressin Antagonists: Clinical Indications

<table>
<thead>
<tr>
<th>V1a Antagonist</th>
<th>V2 Antagonist</th>
<th>V1a/V2 Antagonist</th>
<th>V1a/V1b or V1b Antagonist</th>
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<tbody>
<tr>
<td>Stress-related disorders</td>
<td>Congestive Heart Failure</td>
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<td>Hypertension</td>
<td>Anxiety</td>
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<td>SIADH</td>
<td>Brain edema</td>
<td>PTSD</td>
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<td>Liver cirrhosis w/ ascites &amp; water retention</td>
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<td>Depression</td>
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<td>Nephrotic syndrome</td>
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<td>HPA axis disorders</td>
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<td>Dysmenorrhea</td>
<td>Brain edema</td>
<td>Glaucoma</td>
<td>ACTH-secreting tumors</td>
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<td>Premenstrual Syndrome</td>
<td>Diabetic nephropathy</td>
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<td>Cushing’s Syndrome</td>
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<td>PMDD</td>
<td>Meniere’s</td>
<td>Diabetic nephropathy</td>
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<td>Raynaud’s Disease</td>
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<td>CHF</td>
<td>Hypertension</td>
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<tr>
<td>Motion sickness</td>
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</table>
Major Depression: Symptoms

- Anhedonia
- Blunted Affect
- Disturbed Sleep
- Weight Gain/Weight Loss
- Compromised Social Interactions
Elevated Vasopressin is Linked to Stress-related Disorders: Rodent Model

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

Bunck et al. (2009)

Biological Sciences
Improved Social Interaction Behavior Following Treatment with a Novel Vasopressin Receptor Antagonist vs. Chlordiazepoxide after Chronic Stress

**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)

Meynen et al. (2006)
Biological Sciences
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

Imaging Protocol

ferret

ferret

5 min stimulus

5 min control

Physiology

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

Biological Sciences

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
- Comparable results were obtained with SRX246

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)
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
D. Drug Development
Estimated Costs for Bringing a New Chemical Entity to Market

*All R&D costs (basic research and preclinical development) prior to initiation of clinical testing
**Based on a 5-year shift and prior growth rates for the preclinical and clinical periods.

DiMasi and Grabowski (2007)
Drug Development Process

Discovery, Screening, R & D

FDA IND Review
Avg. 6.5yrs

30 days

FDA evaluates submission

Phase I

Clinical Trials

Avg. 1.5yrs

Avg. 2 yrs

Phase II

Avg. 3.5yrs

Phase III

FDA NDA Review
Avg. 1.2yrs

New Drug Launch

Post Market Activity

Develop Manufacturing and Marketing Plan

FDA Monitors Company Compliance
Biopharmaceutical Drug Development: Attrition

Drug Discovery: 10,000 Compounds
- 5 years

Pre-Clinical: 250 Compounds
- 1.5 years
- IND Submitted

Clinical Trials:
- Phase I: 20-100 Volunteers
- Phase II: 100-500 Volunteers
- Phase III: 1000-5000 Volunteers
- 6 years

FDA Review: NDA Submitted
- 2 years

Large Scale Manufacturing/Phase IV: 1 FDA Approved Drug
- 2 years

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<tr>
<th>Year</th>
<th>Drug Name</th>
<th>Trade Name(s)</th>
<th>Type</th>
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<tbody>
<tr>
<td>1986</td>
<td>Fluvoxamine</td>
<td>Luvox; Solvay</td>
<td>SSRI</td>
</tr>
<tr>
<td>1987</td>
<td>Fluoxetine</td>
<td>Prozac; Lilly</td>
<td>SSRI</td>
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<tr>
<td>1992</td>
<td>Sertraline</td>
<td>Zoloft; Pfizer</td>
<td>SSRI/NRI</td>
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<tr>
<td>1993</td>
<td>Venlafaxine</td>
<td>Effexor; Wyeth</td>
<td>SSRI/NRI</td>
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<tr>
<td>1996</td>
<td>Bupropion</td>
<td>Wellbutrin; Wyeth</td>
<td>SNRI/DRI</td>
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<td>2002</td>
<td>Escitalopram</td>
<td>Lexapro; Forrest</td>
<td>SSRI</td>
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<tr>
<td>2004</td>
<td>Duloxetine</td>
<td>Cymbalta; Lilly</td>
<td>SSRI/NRI</td>
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<tr>
<td>2008</td>
<td>Desvenlafaxine</td>
<td>Pristiq; Wyeth</td>
<td>SSRI/SNRI</td>
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</table>
Discovery & Preclinical Development

- **Lead Selection and Optimization (iterative)**
- **Drug Candidate Confirmation**
- **Preclinical Drug Characterization**

**Efficacy Assessment:** Does it work?

**ADME Profiling:** How can it be delivered and what does the body do?

**Toxicology/Safety Pharmacology Assessment:** Is it safe?

**Pharmaceutics:** Is the manufacture viable and controllable?

Adapted from TetraQ
Stage 1: Lead Selection and Optimization

Essential Pharmaceutics
- Structural Characterization
- Impurity Identification
- Solubility assessment
- Prototype formulation
- Stability testing

Screening Efficacy
- *In vitro* models
- *In vivo* models
- Other

Early ADME
- *In silico* profiling
- Develop simple analytical method
- Measure membrane permeability
- Plasma Stability

Early Toxicology
- Off target screen
- *In vitro* cytotoxicity
- Preliminary AMES
- hERG binding

Adapted from TetraQ
Stage 2: Drug Candidate Confirmation

Data from Lead Optimization Stage

Preliminary CMC (Chemistry, Manufacture and Control)
- Formulation for GLP Toxicology
- Stability testing of active ingredient
- Detailed physicochemical characterization
- Impurity analysis

“Benchmark” in vivo Models
- In vivo models
- Validated models
- Models in other disease areas

ADME Profiling
- Optimized analytical method development
- Basic pharmacokinetics (PK) & Oral Bioavailability
- Determine metabolism of drug

Preliminary Toxicology
- Maximum tolerated dose (MTD)
- Repeat Dose (non-GLP)
- Preliminary Cardiovascular Safety Pharmacology

Adapted from TetraQ
Stage 3: Preclinical Drug Characteristics

Data from Prior Stages

Detailed Preclinical CMC
- ICH Stability Testing
- ICH impurity analysis
- Develop prototype clinical formulation

Comprehensive ADME
- analytical method development
- Comprehensive Pharmacokinetics
- GLP TK
- Comprehensive identification of metabolites

GLP Toxicology Package
- acute study
- subchronic repeat dose study
- Genotoxicity Battery
- Safety Pharmacology

Regulatory Submission or Presentation to Pharma

Adapted from TetraQ
Summary

- Stress-related CNS disorders impact millions world-wide
- Significantly growing economic burden and social effect
- Major need for truly novel medications
- Extended process underlying discovery & clinical development
- New translational models are required to accelerate bench-to-bedside
Thank you for your time and attention