Diseases of the Nervous System

Neal G. Simon, Ph.D.
Professor, Dept of Biological Sciences
Lehigh University
Outline

A. Psychiatric Disorders: Stress-related
   1. Emotional Circuitry: Key Components
   2. The Hypothalamic Pituitary Adrenal (HPA) Axis

B. Neurodegenerative Disorders: Alzheimer’s Disease
   1. Biomarkers & Ethics
Stress-related Psychiatric Disorders: Examples

**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

- 6 million in US
- Current standard of care: no approved treatment, off-label use of SSRIs

**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 (2012); Kessler et al. (2006) ³ NIMH; USAMRMC
Basic Neurobiology & Physiology
Limbic System: Emotional Circuitry

Amygdala: Outputs & Circuits

Price & Drevets (2010)
The Hypothalamic-Pituitary-Adrenal Axis

Key Considerations

- Regulatory Peptides
  - CRF
  - AVP

- Feedback Regulation
  - Glucocorticoids

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

Price & Drevets (2010)
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
Plasma Vasopressin 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).

In veterans with PTSD (far left)
- PTSD w/o MDD
- PTSD with MDD

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).
Predatory Conditioned Fear – A Model of PTSD

sable ferret

Imaging Protocol

- ferret
- 5 min stimulus
- 5 min control

Physiology

- Ferret heart rate
- Blood pressure
- Respiratory rate
V1a Receptor Blockade is Effective in a Conditioned Fear Animal Model of PTSD

- V1a antagonist significantly reduced hyperarousal in brain regions mediating fear & memory when given two weeks after traumatic fear conditioning
- Normal fear responses & arousal patterns were unaffected (not shown)
Functional Neuroimaging in PTSD: Negative Emotional States

AMY: Amygdala
IFG: Inferior Frontal Gyrus
ACC: Anterior Cingulate Cortex
VM PFC: ventromedial prefrontal cortex

Hayes et al 2012
Mood Disorders: Medial Prefrontal Network & Amygdala

Price & Drevets (2010)
Alzheimer’s Disease

- An estimated 5.2 million Americans have Alzheimer's Disease

- 6th leading cause of death in the United States

- $203 billion: the direct costs of caring in the United States in 2013

- In 2050: 14 million people will have AD

- In 2050: $1.2 trillion: direct costs
Alzheimer’s Disease: Symptoms

- Memory loss that disrupts daily life
- Challenges in planning or problem solving
- Difficulty completing familiar tasks
- Confusion with time or place
- Trouble with visual images and spatial relationships
- New problems with words when speaking or writing
- Mood and personality changes
The cortex shrivels up, damaging areas involved in thinking, planning and remembering.

Shrinkage is especially severe in the hippocampus, an area of the cortex that plays a key role in formation of new memories.

Ventricles (fluid-filled spaces within the brain) grow larger.
The Alzheimer’s Brain: Microscopic Changes

- Alzheimer’s tissue has many fewer nerve cells and synapses than a healthy brain.
- PLAQUES, abnormal clusters of protein fragments, build up between nerve cells.
- Dead and dying nerve cells contain TANGLES, which are made up of twisted strands of another protein.
TAU Tangles

A section from the hippocampus of an Alzheimer’s disease patient stained with a tau antibody (TNT1 – recognizes amino acids 2-18, see below). Note the classical triad of tau pathologies in AD, 1) neurofibrillary tangles (arrowheads), 2) neuropil threads (arrows), and 3) a neuritic plaque (asterisk).
Alzheimer’s Biomarkers: Comparison of Clinical Cognitive, Structural, Metabolic, & Biochemical Changes vs. Estimated Expected Years for Symptom Onset

Data shown are differences between mutation carriers and non-carriers

Bateman et al (2012)
Brain scans show evidence of Alzheimer’s disease 20 years before symptoms arise (far left), 10 years before (middle), and after the onset of symptoms (right). Beta amyloid, a protein associated with the disease, is more visible in people who develop the disease (top row) than in those who don’t. The more color in the scan, the more beta amyloid is present in the brain.

Bateman et al (2012)
What Would You Do?
Thank you for your time and attention