Aging Brains, Stress and Alzheimer’s Disease

Kellie L. K. Tamashiro, Ph.D.
Department of Psychiatry & Behavioral Sciences
Overview

• What is Stress?
  – Normal stress response
  – Negative consequences of “toxic” stress

• Aging brain, stress, and cognitive deficit

• Challenge: Find Interventions
What is “Stress”?
The Stress Response

CRH

ACTH

↑ heart rate
↑ blood pressure
↑ respiration
↓ immune function
↓ inflammation
↑ energy mobilization
↓ energy storage
↓ growth
↑ epinephrine release
↑ glucocorticoid release (CORTISOL)
↓ GI function
↓ reproductive function
Stress and Disease

Depression
Anxiety disorders
Cognitive deficits
Post-traumatic stress disorder

Cardiovascular disease
Hypertension
Cancer metastasis
Infection susceptibility
Obesity
Diabetes
Irritable bowel syndrome
Diarrhea
Loss of libido
Sexual dysfunction
Amenorrhea
Impaired fertility
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• Challenge: Find Interventions
Mouse models of stress
Mouse Maze Learning and Memory

Aged mice have severe cognitive deficit after stress

Cordner and Tamashiro, Transl Psych (2016)
Stress Effects on the Brain

- Prefrontal cortex
- Amygdala
- Hippocampus
Hippocampus

Greek for ‘seahorse’
Stress-Induced “Remodeling” of Neurons
Neuron Structure

Aged brain is less able to recover from stress

McEwen & Morrison (2013)
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Cordner and Tamashiro, Transl Psych (2016)
Behavioral Intervention

*Environmental Enrichment ("EE")*

**Standard cage**

- Larger cage area
- Toys to interact with
- Additional bedding material

**Enrichment cage**

- Larger cage area
- Toys to interact with
- Additional bedding material
Mouse Maze Learning and Memory
Performance is preserved with EE intervention

Cordner and Tamashiro, Transl Psych (2016)
Exercise increases size of hippocampus and improves memory in aged adults (65-67 y/o)

Erickson KI et al. PNAS (2011)
Looking to the Future

Brain Plasticity

- **Neurons**: Shrink and expand
- **Connections**: Disappear and are replaced
- **New Neurons**: Continue to grow in some brain areas
Take Home Messages

- Stress is an inevitable part of life.
- The response to stress is a normal and necessary physiological process.
- Chronic stress has deleterious consequences on the brain and cognitive function.
- The aged brain is more susceptible to chronic stress and less able to adapt.
Take Home Messages

• **Basic research** has an important role in studying stress.
  – Study consequences on brain function
  – Identify markers of brain health and function
  – Find interventions against stress and disease
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# Animal Models of Stress

*Depression and Anxiety*

<table>
<thead>
<tr>
<th><strong>Human</strong></th>
<th><strong>Rodent</strong></th>
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<tbody>
<tr>
<td>- Weight loss</td>
<td>- Weight loss</td>
</tr>
<tr>
<td>- Lack of self-care</td>
<td>- Decreased coat quality</td>
</tr>
<tr>
<td>- Lack of energy</td>
<td>- Decreased activity level</td>
</tr>
<tr>
<td>- Anxiety</td>
<td>- Elevated Plus Maze closed arm time/entries</td>
</tr>
<tr>
<td>- Depression (behavioral despair)</td>
<td>- Forced Swim Test immobility</td>
</tr>
<tr>
<td>- Anhedonia</td>
<td>- Decreased sucrose preference</td>
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<tr>
<td>- Cognitive decline</td>
<td>- Barnes Maze performance</td>
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</tbody>
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Whitehall II Study

- Population: British civil servants (~10,500 men and women)
- Varying social status (professional, clerical, manual labor)
- Longitudinal follow-up over 20+ years
- **Inverse** relationship between socioeconomic status and disease morbidity and mortality

EJ Brunner et al. Diabetologia 1997
EJ Brunner Am J Epidemiol 2007
NG Abraham et al., Ann N Y Acad Sci, 2007
Psychosocial Factors and Disease

Linear gradient across socioeconomic status

Morbidity Rate by Socioeconomic Status Level

- Osteoarthritis
- Chronic disease
- Hypertension
- Cervical cancer

Standardized Mortality Ratio, by Occupational Status

- Males
- Females

Socioeconomic Status

- Highest
- Lowest

Occupational Status

- Highest
- Lowest

Occupational Status of Husband

- Highest
- Lowest

Courtesy of Bruce McEwen