Protective and Damaging Effects of Stress Mediators:

Central Role of the Brain

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Central Role of the Brain
In Stress and Adaptation

Many targets for cortisol

Cortisol

Acute - enhances immune, Memory, energy replenishment, Cardiovascular function

Chronic - suppresses immune, Memory, promotes bone Mineral loss, muscle wasting; Metabolic syndrome
Interacting mediators

1. Sympathetic - parasympathetic
2. Sympathetic - inflammation
3. Parasympathetic - inflammation
4. Glucocorticoids - inflammation
5. Metabolism - glucocorticoids
6. Sympathetic - metabolism
7. Metabolism - oxidative stress
Structural plasticity in the adult brain is modulated by experience and hormones.
The Human Brain Under Stress: Role in cognitive function and emotion

Prefrontal cortex
Decision making, working memory, Top down control of impulsive behavior

Hippocampus
Contextual, episodic, spatial memory

Amygdala
Emotion. fear, anxiety, Aggression
The Human Brain Under Stress: Control of the Stress Response

Prefrontal cortex
- Top down control
- Balancing of stress response

Hippocampus
- Shut-off of stress response

Amygdala
- Turns on stress response
Vulnerable to damage. Dendrites shrink with stress

Mossy fiber terminals: glutamate release

Neurogenesis reduced by stress

Glucocorticoids from adrenal via blood

Receptors for glucocorticoids

HIPPOCAMPUS: TARGET OF GLUCOCORTICOIDs plasticity and vulnerability
Molecular Pathways of Remodeling: Present and Future

1. Glucocorticoids
2. Excitatory amino acids - NMDA receptors
3. BDNF
4. Tissue plasminogen activator
5. Polysialated neural cell adhesion molecule [PSA-NCAM]
6. Metabolic hormones
7. Proinflammatory cytokines
8. Biological clocks
Protein/peptide hormones enter and affect the brain

- Leptin: 16kD, excitability, memory, mood
- Ghrelin: 3.5kD, memory, spines
- IGF-1: 7.6kD, neurogenesis, neuroprotection
- Insulin: 5.8kD, glucose transporter, neuroprotection
Brain inflammation and immune tolerance/reactivity: brain dendritic cells and microglia

Aging increases dendritic cell number in cortex, cerebellum, white matter

IL-6 and other inflammatory cytokine receptors are expressed even in normal hippocampus

Dendritic cells become larger with age and show additional activation by systemic inflammation

Dr. Karen Bulloch and colleagues
Rockefeller University
The Human Brain Under Stress: Structural/functional changes

**Hippocampus**
- Contextual, episodic, spatial memory

**Amygdala**

**Hippocampus**

**Cushing's Disease**
**Diabetes**
**Depression**
**Post-traumatic stress disorder**
**Jet lag**
**Sleep deprivation**
**Chronic inflammation**
**Long-term stress**
**Low self-esteem**
Stress causes neurons to shrink or grow
....but not necessarily to die

Control

Chronic stress

Prefrontal Cortex And Hippocampus

Control

Chronic stress

Amygdala

OFC
The Human Brain Under Stress
Structural/functional changes

Amygdala
- Turns on stress response
- Fear learning
- Neurons - increased size after stress in basolateral region
- Overactive in anxiety disorders and depression and after sleep deprivation

Amygdala
Hippocampus
The Human Brain Under Stress
Structural/functional changes

Prefrontal cortex
Neurons shrink with chronic stress

Executive function
Attention shifting - mental flexibility
Extinction of fear conditioning
Working memory
Ability to suppress negative thoughts
Learned helplessness
Autonomic regulation
HPA regulation
Lower subjective social status, as reflected by a lower self-reported ranking on a social ladder, was associated with reduced gray matter volume in the perigenual area of the anterior cingulate cortex (pACC).

STRESS
Central Importance of the Brain and Its Adaptability

Network of interacting mediators

Biphasic actions of mediators - protection vs damage

Many systems simultaneously affected

Central role of the brain and its adaptive plasticity

Loss of resilience?

Cumulative effects and embedding early in life