Stress and the aging brain
Stress and the aging brain: What are the issues?

- Aging makes us less able to adjust to change
- Reactions of elderly to change generate stress
- Stress response involves
  - acute reactions
  - chronic reactions
Acute stress responses

• Sympathoadrenal responses
  • Autonomic functions for emergencies
  • Increased heart rate
  • Vasoconstriction

• Mediated by
  – splanchnic nerves
  – ganglia
  – plexuses

• Neurotransmitter: NE
Acute sympathoadrenal stress responses

- Increased sympathetic tone
- Cardiac manifestations
  - reduced HR variability
- Vascular manifestations
  - reduced vascular compliance
  - hypertension
- Gastric manifestations
  - gastric acid : ulcers
  - ulcerative colitis
Autonomic innervation of the heart

- Parasympathetic (slows down the intrinsic HR)
- Sympathetic (speeds up the resting HR)
Acute sympathoadrenal stress responses

- Adrenal medulla is a rudimentary sympathetic motor nerve
- The second cell produces hormones (80% E, 20% NE) instead of neurotransmitter
- E has actions similar to NE
Brain perception of stress

• Central neural response to stress
  – activation of autonomic reflexes
  – secretion of stress hormones

• Mental distress
  – depression
  – anxiety

• Brain damage inflicted by stress hormones
Central nervous system and stress

• Insular and prefrontal cortex
• Hypothalamus
  – paraventricular and other nuclei
• Limbic forebrain
  – septum
  – hippocampus
• Brainstem nuclei
• Reticular formation
Hypothalamus

- Paraventricular nucleus
  - sympathetic outflow
  - secretion of CRF (HPA axis)
- nuclei controlling homeostatic functions
- nuclei controlling biological rhythms
- nuclei controlling hormone secretion
Hypothalamus and limbic system

- Ventromedial hypothalamus
- Amygdala
- Midbrain & central gray
- Fight-or-flight response
Fight of flight response

- Walter Cannon’s “fight or flight response”
- Sympathoadrenal activation
- Cardiovascular symptoms
- Blanching
- Widening of pupils
- Piloerection
- Sweating
Hypothalamo-pituitary-adrenal axis

- Paraventricular nucleus secretes of CRF (corticotropic releasing factor) into the hypothalamo-pituitary portal circulation
- CRF stimulates secretion of ACTH by the anterior pituitary
Hypothalamo-pituitary-adrenal axis

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Hypothalamo-pituitary-adrenal axis

- ACTH stimulates the adrenal cortex
- Adrenal cortex releases cortisol
- Cortisol has
  - metabolic
  - catabolic
  - anabolic actions
• Cortisol actions
  – metabolic
    • hyperglycemic
    • lipolytic
  – catabolic
    • apoptosis
    • muscle & bone loss
  – immune
  – vascular (after hemorrhage)
  – anabolic actions
    • glycogen synthesis
    • fat synthesis
  – neurotoxic
    • damage to hippocampal neurones
Role of cortisol in chronic stress

• Hans Selye general adaptation syndrome
  – Activation
    • increased glucocorticoid secretion
  – Adaptation
    • Hypertrophy of adrenal cortex
  – Exhaustion
    • Adrenocortical failure
Changes in cortisol secretion in aging

- HPA axis responsivity increases with aging
- Test of cholinergic stimulation of CRF secretion with physostigmine (anticholinesterase)
- Old individuals react more strongly than the young ones
Changes in cortisol secretion in aging

- HPA axis responsivity increases with aging
- Test of cortisol negative feedback in a metyrapone test
- Metyrapone blocks cortisol synthesis
- Cortisol infusion tests cortisol feedback on ACTH production
- Blunted response in the aged
Changes in cortisol secretion in aging

- Although cortisol and ACTH concentrations do not change much with aging
- Sensitivity of HPA axis to stimulation increases
- Glucocorticoids are neurotoxic to hippocampal neurons
- Cognitive function impaired in Cushing’s patients or volunteers receiving cortisol infusions
Types of stressors

• Stressors: conditions that
  – endanger
  – are perceived to endanger

• Types
  – Psychological response to threat
    • fear
    • anxiety
  – Physical stress with psych component
    • pain
    • electric shock
  – Cardiovascular stress
Cardiovascular stresses

• Challenge cardiovascular homeostasis
• Examples
  – hemorrhage
  – orthostatic tilt
  – exercise
  – heat exposure
Cortisol damage to hippocampal neurons

- Neurosecretory cascade
- Hippocampus has high density of glucocorticoid receptors
• Hippocampus is plastic and vulnerable to damage
  – long-term potentiation
  – remodelling of dendrites
  – neurogenesis in dentate gyrus
  – synaptic remodelling
• Site of spatial and declarative memory
• Site of processing of emotional information
• Evidence for neuronal loss in individuals exposed to high cortisol titers
• Genetically vulnerable region
• Apoptosis evidence for cortisol in tissue culture
Neuroprotective role of DHEA

• DHEA in early development
Neuroprotective role of DHEA

- DHEA with aging
Neuroprotective role of DHEA

- DHEA-cortisol ratio with age
Neurotoxic effects of cortisol

- Cortisol and apoptosis
Neuroprotective role of DHEA

- Anti-apoptotic effects of DHEA
Neuroprotective role of DHEA

- DHEA/cortisol ration and depression