Emotional behavior 2

A Syndrome Produced by Diverse Nocuous Agents

Hans Selye

“Experiments on rats show that if the organism is severely damaged by acute nonspecific nocuous agents such as exposure to cold, surgical injury, production of spinal shock (transcision of the cord), excessive muscular exercise, or intoxications with sublethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather a response to damage as such.”

Nature, 1936
“This syndrome develops in three stages: during the first stage, 6–48 hours after the initial injury, one observes rapid decrease in size of the thymus, spleen, lymph glands, and liver; disappearance of fat tissue; edema formation, especially in the thymus and loose retroperitoneal connective tissue; accumulation of pleural and peritoneal transudate; loss of muscular tone; fall of body temperature; formation of acute erosions in the digestive tract, particularly in the stomach, small intestine, and appendix; loss of cortical lipoids and chromaffin substance from the adrenals....”
Stress and the General Adaptation Syndrome

• Hans Selye defined “stress” as the non-specific response of the organism to any demand made upon it.

• General adaptation syndrome: threats (“stressors”) to the body activate a general response to stress.
General Adaptation Syndrome

- Alarm stage: increased sympathetic nervous system activity (acute)
- Resistance stage: sympathetic response declines; adrenal cortex continues releasing cortisol and other hormones to promote alertness
- Exhaustion stage: occurs after chronic, prolonged stress; individual no longer has energy to sustain responses
What is stress?

“stressor” vs “stress” vs “stress response”

Predator attack
Storm
Long drought
Exam
Giving a speech
Spouse with chronic disease
Acute and chronic stressors

• Sympathetic nervous system
  – “fight or flight” responses
  – acute, transient stressors

• HPA axis
  – chronic, prolonged stressors
Discuss with a neighbor:

Acute and chronic stressors at UBC?

How prevalent, frequent, severe?

Consequences of acute or chronic stress?

How to cope with stress? ("good" or "bad" coping strategies)
Acute stress response

• “Fight or flight”
• Increased availability of energy – blood glucose
• Increased oxygen intake
• Increased blood flow to muscles
• Inhibition of digestion, growth and repair, reproduction, pain perception
• Altered immune function
• Enhancement of memory and sensory information
Adrenal medulla

- Catecholamines
  - Epinephrine (adrenaline)
  - Norepinephrine (noradrenaline)
  - Dopamine
Chronic stress can have pathological effects:

- Energy availability: Type 2 diabetes mellitus
- Increase in cardiovascular tone: high blood pressure
- Inhibition of reproduction: infertility
- Inhibition of growth and repair: psychosocial dwarfism, slower wound healing
- Inhibition of immune function: immunosuppression, impaired pathogen resistance
- Stimulation of the CNS: neural degeneration
Chronic stressors

• For humans, many modern stressors are more chronic

• Accounts, in part, for widespread stress-related illnesses and psychiatric problems
(B) Adrenal cortex and medulla

- Aldosterone
- GCs
- DHEA (if ZR is present)
Cholesterol

$\downarrow$ StAR

$\downarrow$ CYP11A1

Pregnenolone

$\downarrow$ CYP17

17$\alpha$-OH-Pregnenolone

$\downarrow$ 3B-HSD

Progesterone

$\downarrow$ CYP17

17$\alpha$-OH-Progesterone

$\downarrow$ 3B-HSD

11-Deoxycorticosterone

$\downarrow$ CYP21

11-Deoxycortisol

$\downarrow$ CYP11B1

Cortisol

$\downarrow$ 11B-HSD1

11-Dehydrocorticosterone

$\downarrow$ 11B-HSD2

18-OH-Corticosterone

$\downarrow$ CYP11B2

Aldosterone

$\downarrow$ CYP11B2

DHEA

Androgens

Estrogens
Adrenal GCs orchestrate an organismal stress response
Hippocampus

- negative feedback to HPA axis
- many glucocorticoid receptors (GR)
  - GR vs. mineralocorticoid receptors (MR)
- chronic stress
  - dendritic atrophy of pyramidal cells
  - cell loss
Chronic stress and dendritic atrophy

Golgi stain

CA3 pyramidal neurons
Dendritic atrophy

Tree shrews
- Prolonged high cortisol levels make neurons in the hippocampus vulnerable to overstimulation and death.
- Hippocampal damage leads to increased cortisol levels...
Unipolar Depression (Major Depressive Disorder)

- Sad & helpless every day for weeks
- Loss of interests, energy, appetite
- Little or no pleasure from eating or sex
- Feel worthless
- Contemplate suicide
- Difficulty in concentrating
- Restless agitation
- Poor memory
Unipolar Depression

• 2X as often in women as in men
• ~5 to 10% of adults have “clinically significant” depression
• leading cause of disability worldwide
• among the most costly of all psychiatric disorders
• A genetic component
  – 60% concordance rate for monozygotic twins
  – 20% concordance rate for dizygotic twins
  – not a single-gene defect
• Medications work in only 60% of cases
• Stress is a major risk factor
Dexamethasone (DEX)

(b) Normal controls

(c) Depressed patients
Immune system

- The goal of the immune system is to defend the body against pathogens and infectious agents such as viruses, bacteria, fungi...and cancer, damaged cells, etc.
- A fundamental aspect of this involves differentiating “self” from “non-self”
- This is accomplished primarily by white blood cells (leukocytes)
  - monocytes, lymphocytes, etc.
Types of immunity

• Nonspecific (innate) immunity
  – Rapid, first line of defense, monocytes and macrophages
  – Destroys anything “non-self”
  – But in the process, can also damage “self”

• Specific (adaptive) immunity
  – Takes time to develop
  – Cell-mediated immunity
    • Involves T cells (type of lymphocyte)
    • Kills specific pathogens upon re-exposure to a pathogen
  – Antibody-mediated (humoral) immunity
    • Involves B cells (type of lymphocyte)
    • Production of antibodies upon re-exposure to a pathogen
Lymphocytes

- Lymphocytes originate in the bone marrow.
- Those that mature in the bone marrow are termed B cells and participate in antibody-mediated (humoral) immunity.
- Antibodies: Y-shaped proteins that attach to particular kinds of antigens.
- Antigens: proteins on cells, viruses etc.
- Antibody-tagged cells are destroyed by macrophages etc.
Lymphocytes

• Some lymphocytes migrate from the bone marrow to the thymus
• Lymphocytes that mature in the thymus are termed T cells and participate in cell-mediated immunity
• Attack pathogens directly (cytotoxic T cells) and also help other T cells or B cells to multiply (helper T cells)
Cytokines

- During an infection, leukocytes and other cells produce small proteins called cytokines
  - combat infection and inform brain

- Cytokines stimulate the release of prostaglandins
  - produce fever, sleepiness → conserve energy
Cell-mediated immunity

T helper

Interleukin-1

Macrophage

Interleukin-2

Infectious agent

C

T

T

T
Antibody-mediated immunity

Macrophage

Infectious agent

Interleukin-1

T helper

B cell growth factor

B

B

B

B

B

B
Responses to a Bacterial Infection

- Bacteria enter through punctured skin
- Bacteria trigger an inflammatory response
- B cell attaches to a bacterium, leaving the bacterium's antigen exposed
- Helper T cell causes this B cell to divide
- B memory cells differentiate into memory cells prepared to attack the same antigen
- Natural killer cells attack tumors and some other intruders, injecting chemicals that kill them
- Secretions of cytokines
- Circulating antibodies attach to the antigen and mark it for destruction
- Some B cells become plasma cells that secrete antibodies specific to this antigen
Acute vs. chronic effects of stress and GCs