The Immune System: The Mind Body Connection

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Psychoneuroimmunology

“Investigation of the bidirectional linkages between the CNS, the endocrine system, and the immune system, and the clinical implications of these linkages.”

There are clear connections between the physiology that underlies our emotional states and the immune system:

- direct neural connections
- Endocrine connections

A matter of regulation correcting under and over activation
Functions of the Immune system

- Discriminate self from foreign matter
- Destruction and clearance of foreign substances
  - Virus, bacteria, toxins that might enter body, altered self (tumor cells)
- Ignore self - don’t destroy normal cells
- However:
  - **Autoimmune disease**: system attacks itself
    - GI and Joints (rheumatoid arthritis),
Key players of Immune system

- White Blood Cells (leukocytes)
  - Polymorphonuclear granulocytes
    - Neutrophils
    - Eosinophils
    - Basophils
  - Lymphocytes develop in lymph nodes
    - T,
    - Helper- T
    - B
    - Natural Killer (NK) cells
- Monocytes – e.g. macrophages, dendritic cells
Where are they?

- Lymph nodes and vessels
- Bone marrow
- Thymus (T-cells)
- Spleen

- GI tract – to attack food borne pathogens
- Respiratory tract – for air borne pathogens
First line Immune defense: The non-specific Macrophage

- Engulfs and digests foreign organisms
- Displays part of organism on its surface as an antigen
  - Antigen presentation
- This signals other cells of invasion
  - Activates T-cells to duplicate
  - Produce IL-1 that promotes other cell activity
Natural Killer Cells (NK) also nonspecific

- Kills virally infected cells and tumor cells by release of toxic substances into the cells
- “trained” in the
  - Tonsils, spleen, Lymph nodes

- Produces interferon to enhance killing and inhibits viral production
- In vitro, NK kills tumor cells in 3 hrs.
- NK cells taken from stressed animals are less effective than from non-stressed animals
Second line of defense - specific

- Require specificity or fit between immune cell receptor and antigen – pre-programmed
  - **T-cells** are Cytotoxic injects toxins to kill foreigners

- **Helper – T cells**  Enhance function of other cells by release of fluids (IL – 2)
  - Activates T cells

- HIV attacks and kills Helper T cells
Antigen Presentation

1. A phagocyte "eats" a bacteria.
2. Parts of the bacteria (antigen) goes to the surface of the phagocyte.
3. The phagocyte presents the antigen to a helper T cell.
4. The helper T cell is activated.
B- cells Specific targets

- Humoral immunity – secrete protein molecules that coat and neutralize infected cells
  - Immunoglobins - Igs
  - Helps other cells identify and kill infected cells
  - Facilitates NK and T-cell killing
**B-Cells**

1. The B cell finds an antigen which matches its receptors.
2. It waits until it is activated by a helper T cell.
3. Then the B cell divides to produce plasma and memory cells.

4. Plasma cells produce antibodies that attach to the current type of invader.
5. "Eater cells," prefer intruders marked with antibodies, and "eat" loads of them.
6. If the same intruder invades again, memory cells help the immune system to activate much faster.
How can psychological events affect the immune system?

- Classical Conditioning
- Activation of the HPA axis – cortisol secretion
- Activation of the Sympathetic Nervous System - NE
Conditioning the Immune response

- Eating sherbet - Conditioned Stimulus (CS)
  - +
- Injection of NE (increases NK activity) as Unconditioned Conditioned Stimulus (UCS)

- 5 trials, 6th day, CS alone: Eating sherbet, increased NK (CR)
- Controls:
  - saline injection alone – no response
  - eating sherbet alone – no response

- Conditioning can both stimulate and depress immune sys.
Stress affects on Immune System

- HPA axis and cortisol (anti-inflammation)
- Stress causes dysregulated cortisol response
  - Produces too much or too little
  - Short term stressor – raises it

- Long term and long past stresses might result in too low of cortisol – no inflammation suppression
  - Flattens out the diurnal cycle of cortisol production

- Depressed pts. Have blunted cortisol effect – don’t produce enough.
If stress causes Cortisol to be levels high:

- Inversely related to # of lymphocytes in blood
- Impairs immune function by
  - decreasing IL-2
  - Kills WBC
  - Decreases tumor necrosis factor
  - Decreases inflammation response
Stress effects

- Lab stressors (mental arithmetic) that causes NE surges, *increases* NK cell activity. **Short run**
  - Give beta blocker and effects is eliminated
- Other **longer term** stressors including exam stress:
  - Suppresses lymphocyte production (T-cell production
    - NK cell function
  - “production of interferon
  - Reactivates latent viruses – herpes
  - Lower antibody response to vaccinations
Inflammation regulation

- Inflammation process brings immune cells into a damaged area of the body (e.g. cuts) so they can destroy foreign cells:

- **Cytokines** – released by immune cells and regulate immune responses

- **Pro-inflammatory Cytokines (PIC)** from Macrophages coordinate inflammatory responses in body –
  - Tumor Necrosis Factor kills tumors
  - Produce IL-1 which leads to IL-2
  - Stimulate Helper –T to differentiate
  - B- cells to proliferate
  - IL – 6 to produce C-Reactive Protein (a marker of inflam)
Anti-Inflammatory cytokines (IL-10,)

- Cytokines are regulators of host responses to infection, immune responses, inflammation, and trauma.
  
  - Some cytokines act to make disease worse over time (proinflammatory), whereas others serve to reduce inflammation and promote healing (anti-inflammatory).
Stress and inflammations:

- Brief lab stressors increase pro-inflammatory cytokines that can maintain a long term inflammation response.
- Stressors can lead to long term systemic inflammatory responses.
- BUT: does not mean that all systematic inflammations are due to psychological or environmental stressors.
Inflammatory diseases
some are also called autoimmune diseases

- The immune system and the Inflammatory response stays “on” by secreting PIC:
- Inflammatory Bowel Disease - Crohn’s disease
- Rheumatoid arthritis,
- liver and kidney fibrosis
- COPD
- Heart disease / atherosclerosis (inflamed arteries; CRP is marker)
- Some Cancer
- Alzheimer’s Disease;
  - Plaques filled with pro-inflammatory cytokines
Depression and PIC

- Inflammatory diseases associated with Dep.
- Depressed patients have high levels of PIC
  - Cause or effect?
- Injections of PICs cause dep. Sx in healthy people
  - Dysphoria, anhedonia, fatigue, apathy, helplessness
  - PIC cause depression-like syndrome in animals

- Antidepressants reduces PIC in vitro
  - Chronic Rx with anti-deps reduces PICs in animal models
- IS depression related to inflammations??
Immune system and Cancer

- Controversy over role of Immune system in human in vivo cancer

- T-cell and NK cells can kill some tumors in vitro and some can kill in vivo.

- Immune system plays a larger role in controlling tumor metastases than in initiating the tumor

- More an issue of control rather than cause
Animal models (mice) of stress and cancer progression

- Stressed mice with ovarian cancer – tumors grow and spread more quickly
- Hormones from stressed animals bind on receptors on tumors and stimulate angiogenesis - faster tumor growth
  - This effect is blocked with beta blocker – it blocks NE released during stress.

- These have not been replicated in humans
- Need to be cautious in extrapolations to human cancer