Endocrine - Immune Interaction

- Introduction to the immune system: lymphatic system, its immune cellular components and communication signals

- The neuroendocrine - immune link: a reversal of reductionist approaches (e.g. HPA, cortisol, anti-inflammatory effect; PRL, DA, pro-inflammatory effect; steroids and modulation of immune response) underlies the effects of the immune system on CNS as well as of the CNS on the immune system.

- HPA axis and neuroendocrine - immune link: adjuvant-induced arthritis and other models, gonadal steroids and other neuroendocrine systems, disease susceptibility / mechanisms at the central and hypothalamic level

Introduction

“story lines”

For each hormone, the student should know:
1. Its cell of origin
2. Its chemical nature, including:
   a. Distinctive features of its chemical composition
   b. Biosynthesis
   c. Whether it circulates free or bound to plasma proteins
   d. How it is degraded and removed from the body
3. Its principal physiological actions:
   a. At the whole body level
   b. At the tissue level
   c. At the cellular level
   d. At the molecular level
   e. Consequences of inadequate or excess secretion
4. What signals or perturbations in the internal or external environment evoke or suppress its secretion:
   a. How these signals are transmitted
   b. How that secretion is controlled
   c. What factors modulate the secretory response
   d. How rapidly the hormone acts
   e. How long it acts
   f. What factors modulate its action
Introduction

- The immune system
- The endocrine-immune link
- The HPA axis and immune response

The immune system is controlled “from within and from without” as suggested by Medawer 1973.

Introduction

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Multiple immune cells and their secretions regulate the immune response “from within.”

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Multiple immune cells and their secretions regulate the immune response "from within"

Adaptive immunity takes 4 to 7 days to occur but is specific
Innate immunity operates within hours but is nonspecific

Examples:
- Th, DC, APC
- Cells of the immune system and their secretions

Pro-inflammatory response
Th1 / Th2
Anti-inflammatory response
Introduction

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innate immunity operates within hours but is nonspecific. It involves neutrophils and macrophages. Acquired or Adaptive Immunity takes 4 to 7 days to occur but is specific. It involves lymphocytes.

Lymphocytes arise from stem cells in the bone marrow. They differentiate in the primary (central) lymphoid organs—bone marrow and the thymus, and then migrate through the bloodstream to seed secondary lymphoid tissues: lymph nodes, spleen, and lymphoid tissues associated with mucosa. B cells lymphocytes differentiate in the Bone marrow and give rise to plasma cells which secrete antibodies. T cell lymphocytes differentiate in the Thymus and attach directly to target cells to kill them (T-cytotoxic cells and Natural Killer cells) and are important in elimination of tumors and virus-infected cells. Some T cells (T-helper cells) act by secreting soluble short-range molecules called cytokines. Cytokines are immune 'hormones' that typically act in paracrine fashion to control the proliferation, differentiation and activity of immune cells.

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Introduction

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Phagocytes provide innate cellular immunity in tissues. They initiate host-defense responses and provide the first line of defense against microorganisms. Neutrophils, also called polymorphonuclear cells (PMNs) are the most numerous of white blood cells and have a rapid turnover. They possess a multi-lobed nucleus, work well under ischemic conditions, and phagocyte bacteria. Macrophages and Monocytes come from the bone marrow. Monocytes circulate briefly then leave the bloodstream and attach to the walls of sinusoids. There they undergo a series of structural and functional alterations, leading to the formation of tissue macrophages. Mast cells are connective tissue cells found near blood vessels. They have basophilic granules, and release histamine (serotonin in the rat), as well as anaphylaxis, a slow-reacting substance known to increase vascular permeability and edema.

Multiple immune cells and their secretions regulate the immune response “from within”
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Neurotransmitters, hormones and peptides regulate the immune response "from without"

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Neuroendocrine-immune link

The neuroendocrine-immune connection has been driving a reversal of reductionist approaches. Some examples on such a line of thought:

- Berevement, as a starting point of an ongoing trend
- HPA axis, cortisol and its anti-inflammatory effects
- Pro-inflammatory role of PRL and its control by DA
- Pro-inflammatory role of some steroids and action mechanisms of their immune modulatory effects
- Susceptibility to disease and possible mechanisms

Neurotransmitters, hormones and peptides regulate the immune response “from without”
Neuroendocrine-immune link

- The immune system
- The endocrine - immune link
- The HPA axis and immune response

<table>
<thead>
<tr>
<th>Hormones and neurotransmitters in the immune tissue and immune modulators in brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRH, AVP, OT, GnRH, LH, ACTH, POMC, END, ENK, TSH, PRL, SS, GH, Nepi, SP</td>
</tr>
<tr>
<td>IL1, IL6, TNFa, IL3, IFNg, TGF and their receptors</td>
</tr>
</tbody>
</table>

The brain and immune system “talking to each other” is essential for maintaining homeostasis
# Neuroendocrine-immune link

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effect on Inflammation</th>
<th>Effect on Immune System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Androgen</strong></td>
<td>Anti-inflammatory</td>
<td>Receptors present on immune tissues are immuno suppressive on both T and B cells. Decreases thymic mass. Suppresses antibody response. Increases TGFβ inhibition of TH1-mediated functions.</td>
</tr>
<tr>
<td><strong>Estrogen</strong></td>
<td>Pro-inflammatory depending on disease</td>
<td>Receptors present on immune tissue. Decreases thymic mass. Inhibits suppressive T cells. Facilitates T helper lymphocytes maturation. Stimulates B cell mediated antibody response.</td>
</tr>
<tr>
<td><strong>DHEA</strong></td>
<td>Anti-inflammatory</td>
<td>DHEA receptor binding complex present on tissue. Inhibits thymic atrophy induced by cortisol. Suppresses IL6 production. Enhances IL2 production. Inhibits formation of autoantibodies.</td>
</tr>
</tbody>
</table>

The brain and immune system “talking to each other” is essential for maintaining homeostasis.

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<table>
<thead>
<tr>
<th>Neuroendocrine Stimulus</th>
<th>Effect on Immune System</th>
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<tbody>
<tr>
<td><strong>ANS adrenergic stimulation</strong></td>
<td>Inhibits macrophage activity. Stimulates multipotential stem cell development. Stimulates T cell proliferation. Stimulates antibody production from B cells.</td>
</tr>
<tr>
<td><strong>ANS cholinergic stimulation</strong></td>
<td>Stimulates multipotential stem cell development. Enhances T cell proliferation. Stimulates antibody production from B cells.</td>
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### Neuroendocrine-immune link

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<tr>
<td>HPA system ACTH</td>
<td>Inhibits macrophage activity</td>
</tr>
<tr>
<td></td>
<td>Inhibits T cell proliferation</td>
</tr>
<tr>
<td></td>
<td>Stimulates B cells growth but inhibits antibody production</td>
</tr>
<tr>
<td>HPA system Cortisol</td>
<td>Inhibits multipotential stem cell colony formation</td>
</tr>
<tr>
<td></td>
<td>Inhibits T cell proliferation and cytotoxic T cell activity</td>
</tr>
<tr>
<td></td>
<td>Inhibits antibody production from B cells</td>
</tr>
<tr>
<td></td>
<td>Inhibits natural killer cell activity</td>
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### Neuroendocrine-immune link

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<th>Neuropeptide</th>
<th>Effect on immune system</th>
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<tr>
<td>SP</td>
<td>Stimulates phagocytosis by macrophages</td>
</tr>
<tr>
<td></td>
<td>Stimulates T cell proliferation</td>
</tr>
<tr>
<td></td>
<td>Stimulates antibody production from B cells</td>
</tr>
<tr>
<td>SS</td>
<td>Inhibits multipotential cell colony formation</td>
</tr>
<tr>
<td></td>
<td>Inhibits T cell proliferation</td>
</tr>
<tr>
<td></td>
<td>Inhibits antibody production from B cells</td>
</tr>
<tr>
<td>EOP</td>
<td>Inhibits phagocytosis by macrophages</td>
</tr>
<tr>
<td></td>
<td>Stimulates T cell proliferation and cytotoxic T cell activity</td>
</tr>
<tr>
<td></td>
<td>Stimulates (ßEND) or inhibits (ENK) antibody production from B cells (depending on the state of the cell)</td>
</tr>
<tr>
<td></td>
<td>Stimulates natural killer cell activity</td>
</tr>
<tr>
<td>VIP</td>
<td>Inhibits phagocytosis by macrophages</td>
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<td>Inhibits T cell proliferation</td>
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<td>Inhibits natural killer cell activity</td>
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<tr>
<td>VGF</td>
<td>Stimulates cytokine release from T cells</td>
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The brain and immune system “talking to each other” is essential for maintaining homeostasis.
Neuroendocrine-immune link

- The immune system
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Example of complex interactions in a local physiological response involving inputs “from within and from without” (see web endotext file)

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The corticosterone response is not generated against the challenge per se but, rather, is an attempt to regulate the response that is generated to the challenge (disease susceptibility?)

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The neuroendocrine-immune connection has driven a reversal of reductionist approaches.
The neuroendocrine - immune connection has driven a reversal of reductionist approaches.

There is good correlation between the decrease in CRH-mRNA levels in the PVN and the increase in severity of inflammation.

Adjuvant-induced arthritis model: hybridization with a probe complementary to CRH in PVN.
there is a decrease in CRH-mRNA levels in the PVN that occurs despite activation of the HPA axis. With recovery, levels return to those seen in controls and at the preclinical stage.

Allergic encephalomyelitis model: hybridization with a probe complementary to CRH in PVN

A chronic stress model (EAE and EMS)

low CRH and high AVP

Diabetes type 1, a chronic stress model

AUTOANTIBODIES are revealed by green fluorescence in a micrograph of a human islet exposed to blood from a patient with type 1 diabetes. The surrounding area is dark because it lacks islets.
HPA axis and immune response

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Overview/Predictive Antibodies
- In autoimmune diseases, such as type 1 diabetes, the immune system mistakenly manufactures antibodies that target the body's tissues.
- Certain of these "autoantibodies" appear many years before overt symptoms of disease, suggesting that screening for these molecules could be used to predict who is at risk of falling ill.
- Autoantibodies might also serve as guides to disease severity and progression and might even warn of risk for some nonimmune disorders.
- Screening for predictive autoantibodies could one day become routine, although a dearth of preventive treatments currently stands in the way.

Diabetes type 1, a chronic stress model?

Insulin-induced hypoglycemia, an example of homeostatic events set in motion in response to a stressor, to maintain system steady state.
Diabetes Mellitus type 1

Early Autoimmune Attack

HOW DIABETES DEVELOPS
The attack on beta cells begins when immune cells called T lymphocytes and B lymphocytes invade the islets of Langerhans, where the beta cells reside. The T cells probably cause most of the damage (top detail), but as those cells work their magic, the B lymphocytes spit out antibodies against proteins made by beta cells, usually starting with insulin.

As the attack on the islets continues, damaging them severely, other types of autoantibodies may appear, such as those targeted to the proteins IA-2 and IA-2β (bottom detail). The order and time at which the additional autoantibodies arise can vary.

Diabetes Mellitus type 1

HPA axis and immune response

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Autoimmune diseases are examples of homeostatic events set in motion in response to a stressor, to maintain system steady state.
The neuroendocrine - immune connection is another example of “circles interacting with circles”.