Homeostasis

The goal of this lecture/recitation is to discuss the concept of homeostasis and to introduce basic signal transduction mechanisms involved in homeostatic regulation.

The sections for this lecture are:

- **Basic concepts**
- **Homeostasis**
- **Signal transduction**
- **Recitation questions**
  - #01 - #02 and how to approach them

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**Basic concepts**

- **How do we know what we know**
  - reductionism, the most successful experimental approach in physiology
  - life as chemical reactions occurring under linear versus non-linear conditions
  - integrative physiology and non-linear conditions
  - functional genomics, the future of experimental physiology

- **Structure / function relationship and levels of organization**

*Life is a series of chemical reactions occurring in compartmentalized environments.*
Basic concepts

- Communication at cellular and sub-cellular levels
  - Neural communication
  - Endocrine communication
  - Neuroendocrine communication
  - Signal transduction pathways
  - Cross-talk among signal transduction pathways
  - Channels and enzymes as final effectors

- Homeostasis and the concept of feedback regulation

Feedback regulation

- Life runs against a thermodynamic equilibrium
- Energy is used to generate work to keep life alive
- The need of potential energy stores due to sporadic input

- Theoretical components of a feedback loop (“refrigerator”)

- Visualization of a classic motor reflex arc as feedback
- The body thermoregulatory control as example
- Homeostatic processes related to thermoregulation

Life runs against a thermodynamic equilibrium
Feedback regulation

- variable under control (t°F/C)
- thermostat (set point)
- t°F/C detector (feedback)
- comparator (integrator)
- common language
- error signal (on/off)
- amplifier and engine

Chemical reactions are ultimately controlled by negative feedback mechanisms.

Feedback regulation

- visualization of a classic motor reflex arc as feedback
- the body thermoregulatory control as example
- homeostatic processes related to thermoregulation

Chemical reactions are ultimately controlled by negative feedback mechanisms.
Chemical reactions are ultimately controlled by negative feedback mechanisms.

**Feedback regulation**

**TABLE 1—3 Questions to Be Asked About Any Homeostatic Reflex**

1. What is the variable (for example, plasma potassium concentration, body temperature, blood pressure) that is maintained relatively constant in the face of changing conditions?

2. Where are the receptors that detect changes in the state of this variable?

3. Where is the integrating center to which these receptors send information and from which information is sent out to the effectors, and what is the nature of these afferent and efferent pathways?

4. What are the effectors, and how do they alter their activities so as to maintain the regulated variable near the set point of the system?

Chemical reactions are ultimately controlled by negative feedback mechanisms.
thermoregulation

homeostatic processes related to thermoregulation

\[ S \sum E \]

chemical reactions are ultimately controlled by negative feedback mechanisms
Feedback regulation

What is fever?

Chemical reactions are ultimately controlled by negative feedback mechanisms.

Fever is caused by an increase in the set-point value of the thermoregulatory system.
Homeostasis

Homeostasis, or constancy of the internal environment, is needed for chemical reactions underlying life to occur. It is maintained, predominantly, through negative feedback mechanisms.

Integrators compare what it should be with what it actually is and generate an error signal.

Comparator/integrator

Error signal

Amplification

Effectors mechanism

Effect

Homeostasis, or constancy of the internal environment, is compared with what it should be (info from set-point) in a comparator/integrator, which generates an error signal.

Integrators

Error

S

E

TABLE 1–2 Some Important Generalizations About Homeostatic Control Systems

1. Stability of an internal environmental variable is achieved by balancing inputs and outputs. It is not the absolute magnitudes of the inputs and outputs that matter but the balance between them.

2. In negative feedback systems, a change in the variable being regulated brings about responses that tend to move the variable in the direction opposite the original change—that is, back toward the initial value (set point).

3. Homeostatic control systems cannot maintain complete constancy of any given feature of the internal environment. Therefore, any regulated variable will have a more-or-less narrow range of normal values depending on the external environmental conditions.

4. The set point of some variables regulated by homeostatic control systems can be reset—that is, physiologically raised or lowered.

5. It is not always possible for everything to be maintained relatively constant by homeostatic control systems in response to an environmental challenge. There is a hierarchy of importance, such that the constancy of certain variables may be altered markedly to maintain others at relatively constant levels.
Homeostasis

integrators compare what it should be with what it actually is and generate an error signal
Homeostasis

Categories of Chemical Messengers

(how components of homeostatic control systems talk to each other)

most communication strategies involved a ligand binding to a receptor

Intercellular communication

most communication strategies involved a ligand binding to a receptor
### TABLE 5-1 A Glossary of Terms Concerning Receptors

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor</td>
<td>A specific protein in either the plasma membrane or the interior of a target cell with which a chemical messenger combines, and which then invokes a biologically relevant response in that cell.</td>
</tr>
<tr>
<td>Specificity</td>
<td>The ability of a receptor to bind only one type or a limited number of structurally related types of chemical messengers.</td>
</tr>
<tr>
<td>Saturation</td>
<td>The degree to which receptors are occupied by a messenger. If all are occupied, the receptors are fully saturated; if half are occupied, the saturation is 50 percent, and so on.</td>
</tr>
<tr>
<td>Affinity</td>
<td>The strength with which a chemical messenger binds to its receptor.</td>
</tr>
<tr>
<td>Competition</td>
<td>The ability of different molecules very similar in structure to combine with the same receptor.</td>
</tr>
<tr>
<td>Antagonist</td>
<td>A molecule that competes for a receptor with a chemical messenger normally present in the body. The antagonist binds to the receptor but does not trigger the cell's response.</td>
</tr>
<tr>
<td>Agonist</td>
<td>A chemical messenger that binds to a receptor and triggers the cell's response; often refers to a drug that mimics a normal messenger's action.</td>
</tr>
<tr>
<td>Down-regulation</td>
<td>A decrease in the total number of target-cell receptors for a given messenger in response to chronic high extracellular concentration of the messenger.</td>
</tr>
<tr>
<td>Up-regulation</td>
<td>An increase in the total number of target-cell receptors for a given messenger in response to a chronic low extracellular concentration of the messenger.</td>
</tr>
<tr>
<td>Supersensitivity</td>
<td>The increased responsiveness of a target cell to a given messenger, resulting from up-regulation.</td>
</tr>
</tbody>
</table>

There are intracellular receptors and receptors located in the plasma membrane.

### TABLE 5-2 Classification of Receptors Based on Their Locations and the Signal Transduction Pathways They Use

1. **INTRACELLULAR RECEPTORS** (Figure 5-3) (for lipid-soluble messengers) Function in the nucleus as transcription factors or suppressors to alter the rate of transcription of particular genes.

2. **PLASMA MEMBRANE RECEPTORS** (Figure 5-4) (for lipid-insoluble messengers)
   - a. Receptors that themselves function as ion channels.
   - b. Receptors that themselves function as enzymes.
   - c. Receptors that are bound to and activate cytoplasmic JAK kinases.
   - d. Receptors that activate G proteins, which in turn act upon effector proteins—either ion channels or enzymes—in the plasma membrane.

There are intracellular receptors and receptors located in the plasma membrane.
Signal transduction

There are intracellular receptors and receptors located in the plasma membrane.

Signal transduction

- Chemical messengers and cell function regulation
  - Homeostasis, receptors and results of receptor activation
  - Signal transduction pathways and membrane receptors
  - Signal transduction pathways and intracellular receptors
  - Cross-talk among signal transduction pathways as operational integrators

Life is a series of chemical reactions occurring in compartmentalized environments.
Signal transduction

- cAMP is the most widely distributed 2nd messenger

- the Nobel prize was awarded for the discovery of cAMP and G proteins

- through G protein, receptor is linked to either an enzyme or a channel to express the effect of a bound ligand

- dissociation of GDP and binding of GTP to the alpha subunit is elicited by ligand binding to the receptor

- cAMP regulates cell functions by binding to cAMP-dependent PKA

Life is a series of chemical reactions occurring in compartmentalized environments
• membrane receptors using cAMP
  - stimulate: Rs / Gs: Epi, ACTH, AVP, Ang II, LH, FSH, TSH, 5HT, glucagon
  - inhibit: Ri / Gi: α 2 adrenergic, muscarinic
  - Ach agonists, opioids
  - e.g. FSH on follicles, Ca channels, CREB
  - e.g. glycogen phosphorylase (+) synthetase (-), hormone sensitive lipase (+)
  - e.g. AVP / V2 / Aq3, cystic fibrosis transmembrane regulator (CFTR, Cl channel)
  - e.g. ANP effects (vasodilatation, diuresia natriuresis) through cGMP production keep cation channels open (natriuresis)

• concepts of membrane receptors link to integrators, amplifiers and cross-talk

• There are membrane receptors acting by 2nd messengers other than cAMP

life is a series of chemical reactions occurring in compartmentalized environments
Signal transduction

Life is a series of chemical reactions occurring in compartmentalized environments.
Signal transduction

Life is a series of chemical reactions occurring in compartmentalized environments

Other membrane receptor pathways use tyrosine-kinase enzyme instead of AC (cAMP) or PLC (IP3 + DAG).

- NH2 terminal = receptor
- COOH terminal = enzyme
- JAK kinases
Signal transduction

- Other membrane receptor pathways use gases as neural messengers.

- Glutamate (NMDA receptor) → Calmodulin + Ca → NOS active (arginine → citrulline) → NO → NO - Fe guanylyl cyclase → GTP → cGMP → physiological response.

- Signal transduction is a series of chemical reactions occurring in compartmentalized environments.

**Adenylate cyclase**
- ACTH, ßadrenergic Cas(Gs), LH, HCG, FSH, Glucagon, PGs, PTH, TSH, alpha adrenergic (Gi), SS

**Guanylate cyclase**
- ANP (ANF)

**Phosphoinositol turnover and Ca flux**
- Ach receptor (muscarinic), alpha adrenergic Cas, Ang II (also activates Tyr-kinase), LHRH (GnRH), TRH, AVP

**Receptor protein tyrosine kinase (mitogenic pathway)**
- Insulin, IGF, EGF, CSF, FGF

**Receptor - associated tyrosine kinase (cytokine pathway)**
- GH, PRL, EPO, Interleukins, NGF, T-cell receptors

**Ion channels**
- Ach receptor (nicotinic), GABA

Life is a series of chemical reactions occurring in compartmentalized environments.
Signal transduction

**TABLE 5-5** Reference Table of Important Second Messengers

<table>
<thead>
<tr>
<th>SUBSTANCE</th>
<th>SOURCE</th>
<th>EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Enters cell through plasma membrane ion channels or is released from endoplasmic reticulum</td>
<td>Activates calmodulin and other calcium-binding proteins; calcium-calmodulin activates calmodulin-dependent protein kinases. Also activates protein kinase C.</td>
</tr>
<tr>
<td>Cyclic AMP (cAMP)</td>
<td>A G protein activates plasma membrane adenyl cyclase, which catalyzes the formation of cAMP from ATP</td>
<td>Activates cAMP-dependent protein kinase (protein kinase A)</td>
</tr>
<tr>
<td>Cyclic GMP (cGMP)</td>
<td>Generated from guanosine triphosphate in a reaction catalyzed by a plasma membrane receptor with guanylyl cyclase activity</td>
<td>Activates cGMP-dependent protein kinase (protein kinase G)</td>
</tr>
<tr>
<td>Diacylglycerol (DAG)</td>
<td>A G protein activates plasma membrane phospholipase C, which catalyzes the generation of DAG and P, from plasma membrane phosphatidylinositol bisphosphate (PIP2)</td>
<td>Activates protein kinase C</td>
</tr>
<tr>
<td>Eicosanoids</td>
<td>Generated from arachidonic acid in plasma membrane; arachidonic acid is converted into eicosanoids by cytoplasmic enzymes</td>
<td>Paracrine and autocrine effects, such as smooth muscle relaxation</td>
</tr>
<tr>
<td>Inositol trisphosphate (IP3)</td>
<td>See DAG above</td>
<td>Releases calcium from endoplasmic reticulum</td>
</tr>
</tbody>
</table>
Signal transduction

Life is a series of chemical reactions occurring in compartmentalized environments.
First recitation question

The goal of the first two lectures was to review pre-requisite material for this course and to provide students with an overview of the material to be covered in the course. In addition, the first two lectures provided an introduction to the recitation section of the course.

The topics for these two lectures were:

- Physiology, homeostasis, integrators and signal transduction mechanisms
- Review: energy and cells
- Review: structure of a cell
- Review: chemical reactions
- Review: from genes to protein
- Structure, function and examples of biological membranes

Life is a series of chemical reactions occurring in compartmentalized environments.

The main purpose of life is to keep itself alive

Physiology, the study of how life works, is based on the simultaneous occurrence of the following three concepts:
- levels of organization
- structure / function relationship
- homeostatic regulation

Turn each topic into a question, answer it and edit it into one punch line
Select a set of questions you think might be relevant to the information provided in the pre-requisite material for this course. Rank them in order of importance. This questions will serve you as “guides” when editing the information.

Write short paragraph (less than 10 sentences) as your answers to the questions you have just ranked, and start editing the answers.

Turn each paragraphs into a single sentence, if possible.

Rank these single sentences in order of importance.

From all information available to you related to the first 2 lectures: first 6 chapters of textbook, slides in the course website, your lecture notes:

First recitation question

What is life ?
What is physiology ?
How is life maintained ?
What is structure - function ?
What is energy, where does it comes from, how is it used and how is it controlled ?

Energy is the capability to do work.
Energy originates from the sun, it is stored in chemical bonds of macromolecules and it is readily available from cellular ATP.
Use of physiological sources of potential energy is regulated by enzymatic control of intermediary metabolism (nt & hormones).
Specific cells, tissues, organs & organisms have evolved biological structures in order to optimized the use of energy for specific functions (e.g. muscle vs mucosa cell).
A main source of potential energy is the ionic difference across plasma membranes.
First recitation question

What is life?
What is physiology?
How is life maintained?
What is structure-function?
What is energy, where does it come from, how is it used and how is it controlled?

Life, whose only purpose is to keep being alive, is based on enzyme-driven chemical reactions, in compartmentalized environments.

Second recitation question

Select a physiological system or homeostatic event you might use to answer the 4 sub-questions required for most of the recitation questions.

This is a “training” question for you to practice answering most of the recitation questions.

From all information available to you related to the first 2 lectures: first 6 chapters of textbook, slides in the course website, your lecture notes:

- Name the structure (S) and function (F) in your example.
- How do you know these S and F are related.
- What is the story line of your S and F in your example.
- What are the main negative feedbacks involved in your example.