Hormones & Chemical Signaling

Part 2 – modulation of signal pathways and hormone classification & function

Communication
Modulation of Signal Pathways

• How are these pathways controlled?
  – Receptors are proteins!
    • Subject to
      – Specificity of binding
      – Competition for binding site
        » Agonists and antagonists
      – Saturation of ligand
        » Up regulation and down regulation of receptors
  – Pathways are mechanisms under homeostasis guidelines

• Specificity of Binding & Competition
  – Receptors have specific binding sites
  – Different compounds with similar molecular regions may bind to same site = competition
  – Ex. Epinephrine & norepinephrine have similar ligand structure and bind to a class of receptors called adrenergic receptors
    • Adrenergic receptors exhibit specificity
    • Adrenergic receptors are influence by competition
Communication
Modulation of Signal Pathways

• Advances in medicines
  – Due to study of active sites and their properties
    • Slightly changing the non-binding areas may change the duration of action

Communication: Deadly Effects

• Muscarinic receptors
  – Bind acetylcholine (Ach) in the autonomic nervous system (ANS)
  – Also binds muscarine (a mushroom toxin) that
    • Mimics Ach (agonistic action) and can cause a severe parasympathomimetic to the point of death

• Nicotinic receptors
  – Bind Ach at neuromuscular junctions
  – Also binds curare (poison arrow frog toxin) and blocks the receptor (antagonistic action)
    • Causes paralysis and very potentially death

Communication
Modulation of Signal Pathways

• Agonists vs. Antagonists
  – Agonists bind and cause activation
  – Antagonists bind and stop or prevent activation

Communication
Modulation of Signal Pathways

• Up and Down-Regulation
  – Why?
    • To allow cells the ability to control the extent of signal pathway effect depending on
      – The concentration of signal in the ECF
      – The needs of the cell
      – Which form of diabetes would result in up and down regulation of insulin receptors?
  • Down-regulation vs desensitization
    – Down regulation is slower as cell needs to remove receptors from membrane
    – Desensitization is quicker as a binding agent can deactivate the receptor
      » For ex. adding a phosphate can deactivate a receptor (β adrenergic receptors)
Communication
Modulation of Signal Pathways

• When the process has to stop
  – Enzymatic degradation of ligand
  – Removal of ligand by re-uptake
  – Endocytosis of receptor-ligand complex
    • Receptors can be reinserted into the membrane
• Why do we care about this process?
  – Disease & Disorders

Communication
Pathways

• Controlled by homeostatic mechanisms regardless of type of pathway and resulting transduction of signal.

• What are the options for getting the signal to the cell for transduction?

**Table 6-3**  Some Diseases or Conditions Linked to Abnormal Signaling Mechanisms

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>PHYSIOLOGICAL ALTERATION</th>
<th>DISEASE OR CONDITION THAT RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressin receptor (K-linked defect)</td>
<td>Shorter half-life of the receptor</td>
<td>Congenital diabetes insipidus</td>
</tr>
<tr>
<td>Calcium sensor in parathyroid gland</td>
<td>Fails to respond to increase in plasma Ca²⁺</td>
<td>Familial hypocalciemia</td>
</tr>
<tr>
<td>Rhodopsin receptor in retina of eye</td>
<td>Improper protein folding</td>
<td>Retinitis pigmentosa</td>
</tr>
<tr>
<td>Toxins affecting signal pathways</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCKN</td>
<td>PHYSIOLOGICAL EFFECT</td>
<td>CONDITION THAT RESULTS</td>
</tr>
<tr>
<td>Bordetella pertussis toxin</td>
<td>Blocks inhibition of adenylate cyclase (i.e., keeps it active)</td>
<td>Whooping cough</td>
</tr>
<tr>
<td>Cholera toxin</td>
<td>Blocks enzyme activity of G proteins; cell keeps making cAMP</td>
<td>Ions secreted into lumen of intestine, causing massive diarrhea</td>
</tr>
</tbody>
</table>

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Communication Pathways

- Similarities between neural and endocrine pathways?

<table>
<thead>
<tr>
<th>TABLE 6-4 Comparison of Neural and Endocrine Reflexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROPERTY</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Nature of the signal</td>
</tr>
<tr>
<td>Speed</td>
</tr>
<tr>
<td>Duration of action</td>
</tr>
<tr>
<td>Coding for stimulus intensity</td>
</tr>
</tbody>
</table>

Communication Pathways

- The homeostatic pathways are

<table>
<thead>
<tr>
<th>TABLE 6-5 Comparison of Neural, Neuroendocrine, and Endocrine Reflexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENSOR or RECEPTOR</td>
</tr>
<tr>
<td>Afferent pathway</td>
</tr>
<tr>
<td>Integrating center</td>
</tr>
<tr>
<td>Effector(s)</td>
</tr>
<tr>
<td>Response</td>
</tr>
</tbody>
</table>

Communication Hormones

- What are they?
  - Chemical messengers secreted by specialized cells
    - from isolated endocrine cells which makes up the diffuse endocrine system
    - from neurons
    - from immune system cells producing cytokines
  - Where do they go?
    - Into blood (most)
    - Into environment (ectohormones or pheromones)

Communication Hormones

- Involved in
  - Growth
  - Development
  - Metabolism
  - Reproduction

- Act by
  1. Altering rates of enzyme mediated reactions
  2. Control the movement of molecules across the plasma membrane
  3. Regulating the rate of gene expression (& therefore protein production)
Communication

Hormones

- How do hormones get from point A to B?
  - To be classified as hormone & not a paracrine or autocrine hormone
  - Travel in blood
    - May require water soluble (protein) transport mechanism if hormone is lipid soluble

- Hormones act by binding to receptor on target cells
- Hormones have to have a mechanism for ending the effect
  - Stop/reduce production of hormone
  - Degrade hormones
  - Enzymatic removal from receptor
  - Endocytosis of receptor-hormone complex

Communication

Hormone Classification

- Hormones are mainly classified by
  - Source
  - Structure
Communication
Hormone Classification

- Hormones classified by structure
  - Peptide/protein hormones
  - Steroid hormones
  - Amino acid based hormones
    - Derived from tyrosine and may be
      - Catecholamines
      - Thyroid hormones

Communication
Hormone Classification

- Peptide/protein hormones
  - Classification that includes most hormones
  - If a hormone is not a steroid hormone or an amino acid derived hormone, then it is a protein/peptide hormone!
  - Concerns with these hormones
    - How they are made, stored and released
    - How they are transported in blood
    - The mechanism of action
    - How long they last

Communication
Hormone Classification

- Peptide/protein hormones & how they are made, stored and released

Communication
Hormone Classification

(e) Prohormones may contain several peptide sequences that have biological activity

Communication
Hormone Classification

(e) The peptide chain of insulin’s prohormone folds back and is cleaved into insulin & C-peptide
Communication
Hormone Classification

• Peptide/protein hormones
  – Cellular action mechanism
    • Lipophobic – must bind to receptors on membrane’s ECF surface
    • Most work via cAMP messenger system
    • Some via receptor-enzyme complexes
      – Enzyme attached and activated by binding is tyrosine kinase (recall these enzymes phosphorylate various substrates)
        » Insulin binds, tyrosine kinase activated and phosphorylates glucose to glucose 6-phosphate

• Duration
  • Depends on method of hormone action termination
  • Depends on molecule (some synthetic hormones have been modified to last longer)

Communication
Hormone Classification

• Steroid Hormones
  – Lipophilic – creates problems
    • No storage
    • Production is on an “as needed” basis
    • Can have the precursors in cytoplasm ready to go
    • Require protein transports in blood
      – prolongs duration of hormone
      – Blocks entrance into cell… it must disengage from carrier this follows law of mass action…

• Based on cholesterol
• Produced using SER in the
  • Adrenal cortex
  • Gonads
  • Placenta
• Secretion is by simple diffusion
Communication
Hormone Classification

• Steroid Hormones
  – Cellular mechanism of action
    • Diffuses into cytosol and into the nucleus
    • Acts as a transcription factors in the nucleus to alter gene activity by
      – Repressing or activating rates of transcription
      – Lag period due to the processes that have to occur
    • Transcription factors have DNA binding domains (DBDs) that tells them where to bind on the DNA (there are approx. 2000 known human transcription factors with specific DBDs)
    • How are they regulated?
      – Negative feedback loop – increased transcription factors cause a decrease in production
      – Phosphorylation – may stop transcription
      – Ligand binding to transcription factors or cofactors that regulate the transcription factors...

• New(er) research indicates that some steroid hormones have membrane receptors and signal transduction pathways similar in process to peptide/protein hormones
  – Nongenomic actions also attributed to aldosterone and estrogen

Amino acid derived hormones may be
  – Derived from tyrosine
  – Produces
    • T₃ & T₄
    • Epinephrine & norepinephrine
Amino acid derived hormones may be
- Derived from tyrptophan
- Produces
  - Melatonin
  - Serotonin*

*serotonin is classified as a neurohormone as it is synthesized and secreted by neurons of the GI tract for regulation of motility and CNS

Hormones are controlled by reflex pathways most utilizing negative feedback loops!
- May have multiple controls though