Q: Why do vertebrates have an endocrine system?

A: Although it allows extremely rapid communication the “hard wiring” of the nervous system is too “expensive”, inefficient (and unnecessary) for the delivery of molecular signals to every cell in the body.

The cardiovascular system, which is mostly devoted to transporting oxygen and nutrients, can also provide a highly efficient, but relatively slow system for delivering “soluble” messenger molecules to essentially every cell in the body.

However, to ensure fidelity and specificity of the signalling process these “soluble messengers” must be guided to the correct destination by a “molecular address”.

Summary of the major components of the endocrine system:

- Anterior lobe of pituitary
- Posterior lobe of pituitary
- Adrenal cortex
- Pancreas
- Parathyroid gland
- Endocrine system
- Target tissues
- Feedback loops
HORMONES HAVE VARIABLE IN VIVO "STABILITY"

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>Tt</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>3h</td>
</tr>
<tr>
<td>CORTISOL</td>
<td>70 min</td>
</tr>
<tr>
<td>ALDOSTERONE</td>
<td>70 min</td>
</tr>
<tr>
<td>LH</td>
<td>60 min</td>
</tr>
<tr>
<td>ACTH</td>
<td>15 min</td>
</tr>
<tr>
<td>ADH</td>
<td>8 min</td>
</tr>
<tr>
<td>INSULIN</td>
<td>5-8 min</td>
</tr>
<tr>
<td>OXYTOCIN</td>
<td>3-5 min</td>
</tr>
</tbody>
</table>

POTENTIAL REASONS FOR VARIABLE STABILITY

- STEROIDS ARE HYDROPHobic AND MAY PARTITION INTO MEMBRANES AND ADIPOSE TISSUE
- HORMONE CLEAVED BY SPECIFIC PEPTIDASES IN PLASMA
- HORMONE FORMS COMPLEX WITH BINDING PROTEIN WHICH PROTECTS IT FROM DEGRADATION
- SHORT PEPTIDES ARE PARTICULARLY VULNERABLE TO DEGRADATION BECAUSE THERE ARE FEW CONSTRAINTS ON THEIR CONFORMATION

INTRACELLULAR RECEPTORS—"LIGAND-ACTIVATED TRANSCRIPTION FACTORS"

HORMONES WITH INTRACELLULAR RECEPTORS ARE HYDROPHobic ALLOWING DIFFUSION ACROSS PLASMA MEMBRANE

- HIGHLY VARIABLE TRANSCRIPTION-ACTIVATION DOMAIN
- HIGHLY CONSERVED (38 AMINO ACID) DNA-BINDING DOMAIN CONTAINING TWO "ZINC FINGERS"
- CONSERVED (60 AMINO ACID) HORMONE BINDING DOMAINS

CELL SURFACE RECEPTORS REQUIRE TRANSMEMBRANE SIGNALLING

- POLYPEPTIDE HORMONES ARE HYDROPHobic AND CANNOT DIFFUSE ACROSS THE PLASMA MEMBRANE
- THIS PROBLEM IS SOLVED BY UTILISING THE ENERGY OF HORMONE BINDING AT THE CELL SURFACE TO ALTER CONFORMATION OF TRANSMEMBRANE PROTEINS AND THEIR INTERACTIONS WITH INTRACELLULAR PROTEINS

OTHER STEROID HORMONES

GLUCOCORTICOIDS (GR) | PROGESTERONE (PR) | TESTOSTERONE (AR) | ESTROGEN (ER)

STEROID HORMONES BIND TO A SOLUBLE INTRACELLULAR GR RECEPTOR: hsp90 COMPLEX

GLUCOCORTICOIDS Bind TO SPECIFIC SOLUBLE INTRACELLULAR RECEPTORS
REGULATION OF TRANSCRIPTION BY NON-STEROIDAL HORMONES

HORMONE-RESPONSIVE TARGET GENES

VITAMIN D
RETINOIC ACID
THYROID HORMONE

RETINOID X RECEPTOR

SAME HORMONE MAY HAVE DISTINCT EFFECTS IN DIFFERENT TISSUES OR CELL TYPES

EFFECTS ON CELL FUNCTION MAY ONLY OCCUR IF CORRECT COMBINATION OF HORMONES ACT SIMULTANEOUSLY ON SAME CELL.

THE INSULIN RECEPTOR IS A STABLE S-S LINKED DIMER
GROWTH HORMONE AND PROLACTIN RECEPTORS ARE LIGAND-INDUCED DIMERS

IGF-1 USES A SIMILAR MECHANISM
Stat 5A DEFICIENT MICE DO NOT LACTATE
HETEROTRIMERIC G PROTEINS

NUCLEOTIDE EXCHANGE

GDP

GTP

GTPase Activating Protein

GTP

GTP

GAP

Sos

LOW INTRINSIC GTPase

SIGNAL IN

GTP

GTP

GAP

GTPase Activating Protein

GTP

GTP

GAP

GTPase Activating Protein

GTP

GTP

GAP

GTPase Activating Protein

GTP

GTP

GAP

GTPase Activating Protein

GTP

GTP

GAP

GTPase Activating Protein
SYNTHESIS AND SECRETION OF PEPTIDE HORMONES

1. TRANSCRIPTION
2. ALTERNATIVE SPLICING
3. TRANSLATION
4. TRANSLLOCATION
5. TISSUE-DEPENDENT PROTEOLYTIC PROCESSING
6. PACKAGING (200X CONDENSATION) INTO SECRETORY VESICLES
7. SECRETORY VESICLES ACCUMULATE CLOSE TO PLASMA MEMBRANE

REGULATION OF PLASMA GLUCOSE BY INSULIN AND GLUCAGON

GLUCOSE: - SYNTHESIS - MOBILIZATION
PARACRINE INHIBITION OF ISLETS OF LANGERHANS BY INSULIN
GLUCAGON SECRETION
PANCREAS
GLUCOSE: - UPTAKE - UTILIZATION - STORAGE
TARGET TISSUES (liver, muscle, adipose, etc.)

PHYSIOLOGICAL ROLE OF INSULIN
MAINTENANCE OF NORMAL PLASMA GLUCOSE LEVELS IN SPITE OF LARGE CHANGES DUE TO FOOD INTAKE
Rapid uptake of dietary glucose
Stimulation of glucose transport
Stimulation of glucose utilization
Utilization of dietary glucose
Stimulation of glycogen synthesis
Stimulation of glucose oxidation
Stimulation of lipid synthesis
Preservation of energy stores
Inhibition of glycogen degradation
Inhibition of gluconeogenesis
Inhibition of lipolysis
Inhibition of proteolysis

ISLETS OF LANGERHANS

1 MILLION ISLETS EACH CONTAINING ~2500 CELLS
CORE FORMED BY BETA CELLS SECRETING INSULIN (60-70% OF TOTAL)
MANTLE FORMED BY a CELLS SECRETING GLUCAGON (20-25%)
BLOOD FLOWS RADIALLY FROM CENTER OF ISLET TO THE PERIPHERY FACILITATING PARACRINE INHIBITION OF GLUCAGON SECRETION BY INSULIN

RESPONSE OF PLASMA GLUCOSE, GLUCAGON, ACTH AND GROWTH LEVELS TO INSULIN INJECTION

GLUCOSE
GLUCAGON
ACTH
GROWTH HORMONE

GLUCOSE INJECTION MINUTES

REGULATION OF PLASMA GLUCOSE, GLUCAGON, ACTH AND GROWTH LEVELS IN SPITE OF LARGE CHANGES DUE TO FOOD INTAKE
**SYNTHESIS OF THYROID HORMONES: STEP 1 - IODINATION**

1. Iodination
2. Monoiodotyrosine (MIT)
3. Diodotyrosine (DIT)
4. Thyroglobulin

**SYNTHESIS OF THYROID HORMONES: STEP 2 - COUPLING OF IODOTYROSINES**

1. Coupling of iodotyrosine residues results in the synthesis of thyroid hormones.
2. Thyroglobulin synthesis may be regulated by the thyroid.
3. Thyroid hormone synthesis involves the coupling of tyrosine residues in the thyroglobulin molecule.

**THE DEACTIVATION PATHWAY**

1. Values in parentheses indicate peripheral conversion.
2. Thyroid hormone production is regulated by the thyroid gland.

**THYROID HORMONES**

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>RELATIVE POTENCY</th>
<th>PRODUCTION (ug/day)</th>
<th>PLASMA CONCENTRATION (ug/dL)</th>
<th>BOUND TO PROTEINS (%)</th>
<th>t½ (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>+</td>
<td>85-30</td>
<td>8</td>
<td>99.95</td>
<td>6-7</td>
</tr>
<tr>
<td>T4</td>
<td>+ + + +</td>
<td>4.8 (24)*</td>
<td>0.3</td>
<td>99.7</td>
<td>1-3</td>
</tr>
<tr>
<td>rT3</td>
<td>-</td>
<td>2.3 (27)*</td>
<td>0.04</td>
<td>99.8</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Values in parentheses indicate peripheral conversion.
UNREGULATED SYNTHESIS AND SECRETION OF TSH

THYROID DISEASES

<table>
<thead>
<tr>
<th>DISEASE TYPE</th>
<th>THYROID STATUS</th>
<th>SERUM T3</th>
<th>SERUM T4</th>
<th>CAUSE OF DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONGENITAL</td>
<td>HYPO</td>
<td>LOW</td>
<td>HIGH</td>
<td>DEFECT IN IODIDE TRAP OR THYROID HORMONE SYNTHESIS</td>
</tr>
<tr>
<td>IODIDE DEFICIENCY</td>
<td>HYPO</td>
<td>LOW</td>
<td>HIGH</td>
<td>DEFECT IN THYROID TISSUE DUE TO INFLAMMATION</td>
</tr>
<tr>
<td>AUTOIMMUNE: THYROIDITIS</td>
<td>HYPO</td>
<td>LOW</td>
<td>HIGH</td>
<td>AUTOIMMUNODES TO THE TSH RECEPTOR PROVIDE CONTINUOUS UNREGULATED STIMULUS</td>
</tr>
<tr>
<td>AUTOIMMUNE: GRAVES DISEASE</td>
<td>HYPER</td>
<td>HIGH</td>
<td>LOW</td>
<td>UNREGULATED SYNTHESIS AND SECRETION OF T3 AND T4</td>
</tr>
<tr>
<td>THYROID TUMOR</td>
<td>HYPER</td>
<td>HIGH</td>
<td>LOW</td>
<td>UNREGULATED SYNTHESIS AND SECRETION OF TSH</td>
</tr>
<tr>
<td>PITUITARY TUMOR</td>
<td>HYPER</td>
<td>HIGH</td>
<td>HIGH</td>
<td>UNREGULATED SYNTHESIS AND SECRETION OF TSH</td>
</tr>
</tbody>
</table>

IODIDE DEFICIENCY

- LOW IN IODIDE OR (i) IODINE DEFICIENCY
- GOITROGENS PRESENT
- DESTRUCTION OF THYROID TISSUE DUE TO INFLAMMATION
- AUTOANTIBODIES TO THE TSH RECEPTOR PROVIDE CONTINUOUS UNREGULATED STIMULUS
- CONGENITAL SERUM T3 + T4, SERUM TSH
- IODIDE DEFICIENCY
- AUTOIMMUNE: THYROIDITIS
- AUTOIMMUNE: GRAVES DISEASE
- THYROID TUMOR
- PITUITARY TUMOR

Iodide deficiency

- Iodine is essential for the synthesis of thyroid hormones, T3, and T4.
- Deficiency leads to goiter formation due to thyroglobulin accumulation.
- Thyroid gland undergoes hyperplasia in response to the lack of iodine.
- Clinical symptoms include fatigue, weight gain, cold intolerance, and menstrual irregularities.

Autoimmune thyroiditis

- Autoimmune destruction of the thyroid gland
- Leads to hypothyroidism or hyperthyroidism
- Presence of autoantibodies against thyroid antigens

Graves' disease

- Autoimmune thyroiditis associated with high activity of the thyroid gland
- Increased production of thyroid hormones
- Clinical symptoms include weight loss, rapid heartbeat, and heat sensitivity.

Hypothyroidism

- Deficiency of thyroid hormones
- Symptoms include fatigue, weight gain, and cold intolerance.

Hyperthyroidism

- Excess production of thyroid hormones
- Symptoms include weight loss, rapid heartbeat, and heat intolerance.

Calcium in Diet

- Calcium is absorbed in the gut and reabsorbed in the kidney
- Calcium is essential for bone formation and mineralization
- Calcium also plays a role in muscle contraction and nerve impulse transmission.

Calcitonin

- Secreted from the thyroid parafollicular cells
- Acts to reduce serum calcium levels
- Important in maintaining calcium homeostasis

Calcitonin Secretion

- Calcitonin secretion is stimulated by high calcium levels
- Inhibits osteoclast activity, reducing bone resorption
- Increases bone deposition

Calcitonin Response

- Ionized calcium exhibits a steep inverse sigmoidal dependence on extracellular calcium
- Increased calcium suppresses PTH secretion via a G protein-coupled mechanism
- The observation that calcitonin at supraphysiological doses is hypocalcemic led to the mistaken conclusion that it was important for calcium homeostasis.
- Despite these findings, there is no readily apparent pathology due to CT excess or deficiency.

Calcitonin Gene

- The mammalian CT gene is not essential for viability, and its presence may be due to evolutionary considerations.

Hirsch, P.F. and Baruch, H. Endocrine 2003, 201-208