Endocrine Regulation of Reproduction
General Principles

Animal Physiology (Hill, Wise, Anderson):
Ch. 2 — 56-62, Ch. 10 — 260-263, Ch 14 — 390-398
Animal Biology & Biocomplexity

- **Processes**
  - Learning/ Cognition
  - Energy
  - Behavior
  - Immunity
  - Development
  - Reproduction

- **Levels of organisation**
  - Genetics
    - Population/ Environment
    - Organism/Tissues
    - Cell/Molecule
  - Evolution
Endocrinology

- Regulation of ‘milieu interne’
- **Endo**: inside; **crineïn**: secrete
  - Messenger molecules are **hormones** (*horman* - push forward) and **growth factors**
  - Released internally
    - blood
    - intercellular fluid
- Regulate all major physiological processes
  - often together with nervous system
Endocrinology in a Nutshell

• Hormone effects often aim at
  - Homeostasis (keep constant) of ‘milieu interne’
    • temperature, blood glucose …
  - Regulation of developmental processes
    • growth, puberty, reproduction …

Four Steps to Understand Hormones

1 - production
2 - release
3 - receptor
4 - response
Endocrine Regulation of Reproduction

• All animals
  - Local control of germ cells via somatic cells in gonads

• ONLY IN VERTEBRATES
  - Master control over germ cell maturation via Brain-Pituitary-Gonad (BPG) axis

• Sexual reproduction is dangerous
• Adaptational systems evolved to restrict sexual reproduction in time, or suppress it completely, e.g.
  - Puberty: reproduction after somatic maturation
  - Reproductive seasons
The Brain-Pituitary-Gonad System Regulates Reproduction/Fertility

External cues:
- light, temperature
- food, social

GONADS:
- germ cells
- steroids & growth factors

BRAIN:
- puberty
- yearly cycles
- ovarian cycles

PITUITARY:
- LH/FSH

GnRH
Hormones and Spermatogenesis

• Basic research
  - What determines stem cell behaviour?

• Applied research
  - Medical
    ▪ Effect of radiation on spermatogenesis
    ▪ Hormone - receptor interaction in humans
  - Aquaculture
    ▪ salmon and cod: start of pubertal spermatogenesis too early
  - Ecotoxicology
    ▪ Hormone-like contaminants
The Germ Cell Cycle

The genetic sex directs gonadal sex differentiation

The differentiating gonad secretes hormones that determine the phenotypic sex: internal & external genitals, secondary sex characteristics, behaviour, and the endocrine sex.

zygote

adulthood

gonadal sex

Infancy

puberty

phenotypic sex

Genetic sex
Historical Aspects
Back in the Days when …

• Berthold 1849
  - Loss of secondary sexual characteristics & behavior reversed by testis re-implantation
  ➔ testes release biologically active compound in blood

• Starling & Bayliss 1905
  - acid in duodenum ➔ release of secretin into blood ➔ pancreas releases fluid to neutralize acid from stomach; proposed term hormone (horman – aandrijven)

• Takamine 1911
  - purified first hormone: adrenalin (epinephrin)

• Sutherland 1962
  - identified cAMP as first 2nd messenger

• Hormone/growth factor
  - signal molecule that modulates processes in target cells in a specific manner
Endocrine Glands of a Vertebrate

- Place of synthesis
- Biochemistry
  - Amino acid derivatives
    - Thyroxin
  - Oligo/Polypeptides
    - Releasing hormones
    - Insulin
  - Glycoproteins
    - LH/FSH
  - Steroids & alike
    - Steroids
    - Retinoids
Hormone → Receptor
“many ways to Rome”

- **intracrine**
  - receptor in same cell (E2 → ER in Leydig)
Hormone Release

• **Exocytosis**
  - peptides, proteins, glycoproteins, catecholamines
  - fusion of secretory granules with cell membrane

• **Diffusion**
  - steroid hormones
  - Acute synthesis

Figure 14.4 Snapshots of insulin synthesis, processing, and packaging. Insulin, like other peptide hormones, is initially synthesized at ribosomes as an inactive preprohormone and takes its final form through posttranslational processing.
Regulation of Hormone Secretion
Negative Feedback

The 'target organ' can be another endocrine gland, and hence 'the signal' another hormone (typically the case within the BPG axis)
Regulation of Hormone Secretion
Positive Feedback (TRANSIENT!)

Adaptation to a change until a new equilibrium has been reached
Timing of Hormone Secretion: **Pulsatility**

![Graph showing the pulsatility of LH and GnRH secretion over time.](image-url)
Timing of Hormone Secretion: **Daily Rythm**

![Graph showing plasma LH levels with peaks labeled midpuberty and prepuberty.](image-url)
Timing of Hormone Secretion: Monthly

- LH (iU/ml)
- FSH (iU/ml)
- Estradiol (pg/ml)
- Progesterone (ng/ml)

Days from LH peak
Timing of Hormone Secretion: **Incidental**

- **Weather**
  - rainfall induces ovulation in desert parrots
    - plants will flower, providing seeds to feed the young

- **Copulation**
  - vaginal receptors induce ovulatory GnRH secretion surge in many rodents

- **Pheromones**
  - postovulatory females trigger GnRH release in male goldfish
Hormone Action

• Target cell recognizes and binds hormone $[H]$ by means of specific receptor $[R]$

• $[HR]$ becomes, or couples to, signal-generating mechanism

• $[HR]$ or 2$^{nd}$ messenger induces specific changes in target cell physiology

$$[H] + [R] = [HR]$$

$[HR]$ \(\text{2nd messenger}\)

$hormone\ action$
Hormone Receptors: An Overview

- Receptor regulation
  - homologous ➣
  - heterologous ➤
G Protein-Coupled Receptors

- GPCRs
  - Largest gene family in human genome (>1000)
  - Peptides (GnRH)
  - Glycoprotein hormones (LH, FSH)
Receptor (Tyrosine — Serine/Threonine) Kinases

- single TM domain, dimerise upon ligand binding
- activate each others kinase domains by phosphorylation
- associate with downstream signaling molecules
  - ERKs
    - IGF-I
      - maturation of Leydig cells
    - SCF
      - proliferation of spermatogonia
  - SMADs
    - TGFβ: activin, inhibin & AMH
      - Roles both in gonadal organogenesis and adult functioning
Ligands of Nuclear Receptors

- Testosterone
- Estradiol
- Progesterone
- Cortisol
- Aldosterone
- Thyroid hormone
- Vitamin D3
- Retinoic acid
Steroid Action via Nuclear Receptor

1. **Plasma Binding Protein**
   - Steroid
   - Cytoplasm

2. **Target Cell**
   - Activation
   - DNA “Activated”
   - Nucleus
   - New Protein
   - New mRNA
   - “Activated”

3. **Biological Response(s)**
Termination of Hormone Action

- **Target organ**
  - breakdown of cAMP (PDE)
  - dephosphorylation of target proteins
  - re-uptake of Ca^{2+} in ER
  - down-regulation of receptor
    - degradation (fast)
    - ligand-induced, arrestin-dependent internalisation
  - gene expression (slow)

- **Organism**
  - reduced hormone secretion (neg. feedback)
  - increased hormone clearance
  - increased secretion of antagonistic hormone
Termination of Lecturer’s Action
Hormones in Our Environment

- Oestrogens in rivers
  - Male-to-female sex change in fish*
Aquaculture Biotechnology in Norway

- *Stimulate* reproductive success in broodstock animals
- *Inhibit* reproduction in animals to be consumed*