Target cell change its sensitivity to a given stimulus by...

↓

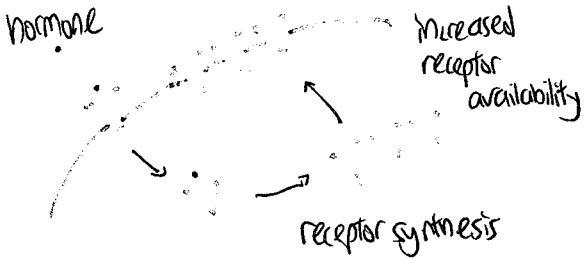
Up & down regulation of receptors

↗ enables an appropriate cellular ~~respon~~ response to be maintained despite ongoing small fluctuations in circulating hormone level

↗ enables the cell to cope w a large & sudden alteration (usually an increase) in circulating hormone

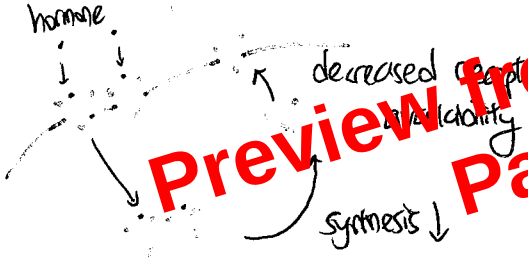
Up-regulation of receptor population:

- binding of hormone to receptor MAY lead to receptor synthesis



Down-regulation of receptor availability:

- binding of hormone may lead to ↓ synthesis of receptor



* Hormone Synergism: The overall effect of a group of hormones is greater than sum of effects of the hormone acting individually on a single cell.

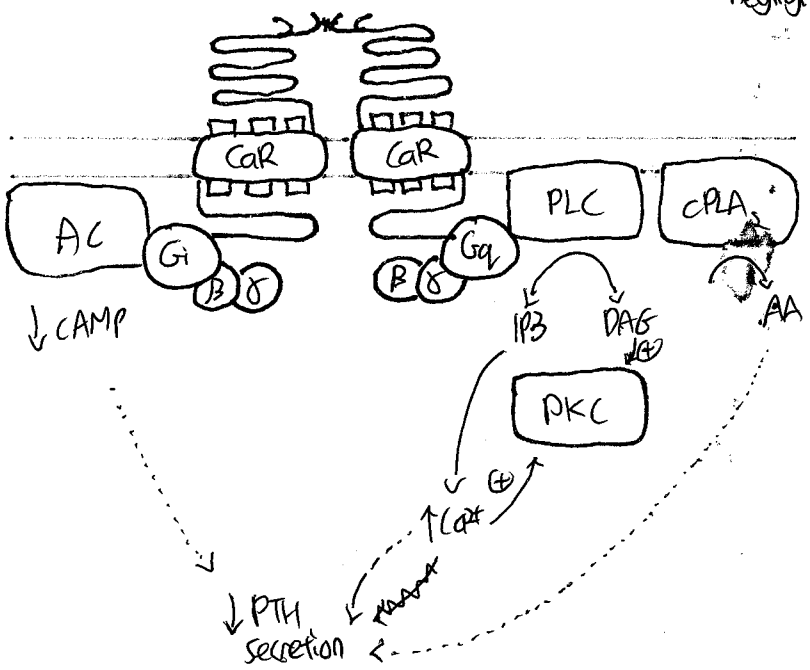
Synergistic interactions between diff. hormones may reflect

- interaction of different signaling pathways
- influence of one hormone on the availability of receptors for a second hormone (up-regulation)

} explanation of hormone synergism

Ca^{2+}-sensing Receptor

hence, effect of Mg^{2+}_o generally negligible ← $[Mg^{2+}_o] < [Ca^{2+}_o]$ in blood (less sensitive)



- CaR is a GPCR responsive to Ca^{2+}_o and Mg^{2+}_o
- Present in kidney where it limits calcium reabsorption
- CaR monitors blood Ca^{2+} levels continuously and serves as the ultimate control point for Ca^{2+} homeostasis

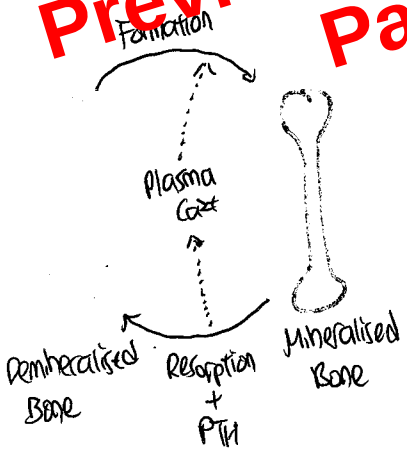
Effects of PTH

↳ PTH elevates plasma $[Ca^{2+}]$ by:
- ↑ Bone resorption
- ↑ renal Ca^{2+} reabsorption ie ↓ excretion, but also ↑ P_i excretion
- ↑ production of $1,25(OH)_2D_3$

Bone Turnover and acute PTH secretion

(through spikes in pulsatile PTH secretion ↑ formation)

* PTH secretion follows a circadian rhythm, hence its pulsatile

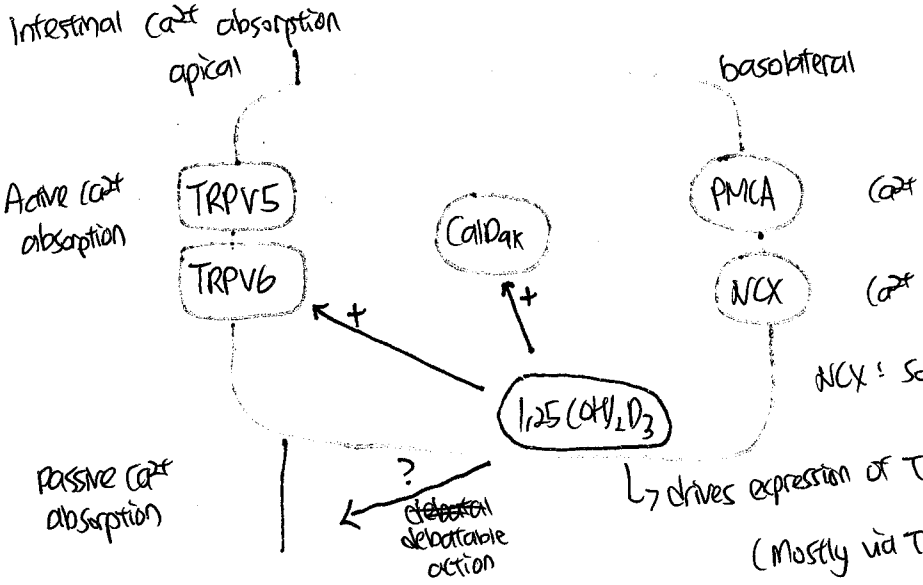


Effects of $1,25(OH)_2D_3$

↳ ↑ net intestinal Ca^{2+} uptake (there are no PTH receptors in gut)

↳ ↑ serum Ca^{2+} levels by ↑ bone resorption and renal Ca^{2+} absorption

Vitamin D receptor (VDR) is a nuclear / intracellular receptor. VDR forms heterodimer with RXR and binds to vitamin D-responsive elements (VDREs) of DNA, regulating transcription of target genes.



NCX: Sodium-calcium exchanger

↳ drives expression of TRPV5, TRPV6, CalDak (mostly via TRPV6)

~ 90% of dietary Ca^{2+} absorption occurs in the small intestine via

a) passive, paracellular diffusion down its electrochemical gradient

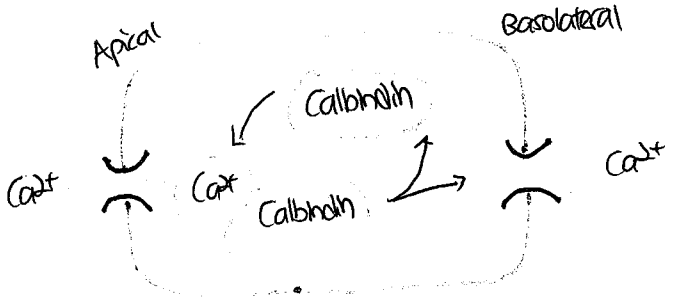
b) active transcellular transport under control of $1,25(OH)_2D_3$

* 28k - 28kDa

Calbindins

- Calbindin-D28k, mainly present in kidney
- D9k, expressed primarily in gut

- calbindin carries Ca^{2+} from apical to basolateral
- Ca absorptive epithelia need protection from mM Ca^{2+} crossing cell $[Ca^{2+}]_i \approx 100nM$
- Calbindin expression substantially dependent on $1,25(OH)_2D_3$
- TRP channels will close when there is insufficient calbindin



The endocrine system responds rapidly to external changes in environment

eg: light/dark (day length), stress, temperature, food supply

How is the link between the nervous and endocrine systems implemented?

The Hypothalamic - Pituitary Axis

↳ central regulatory component of endocrine system

↝ Pituitary gland is directly below the hypothalamus

↝ many hypothalamic hormone secretion are pulsatile, leading to pulsatile secretion from pituitary

Environmental influence

↓

Hypothalamus

↓

Anterior Pituitary

Non-tropic ↓ tropic

Endocrine Gland

↓

Actions on the body

Low temperature

↓

thyrotropin releasing hormone (TRH) [hypothalamic releasing hormone]

↓

thyroid stimulating hormone (TSH)

↓ tropic

thyroid gland

thyroid hormones

↓

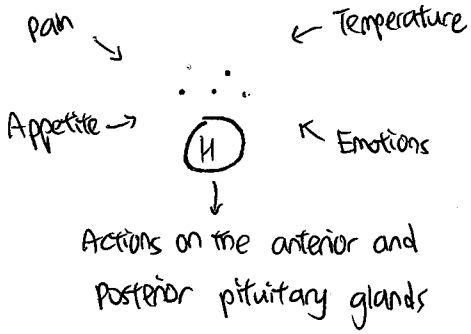
↑ metabolism

↑ heat production

Tropic hormone : hormone that acts on endocrine gland

Non-tropic : hormones that act directly on parts of the body

Diverse chemical messengers within the brain mediate between neurons and the hypothalamus, and may also modulate the actions of each other



The anterior pituitary secretes a range of hormones in response to "releasing hormones" signals from the hypothalamus

Adrenal Gland

↳ adrenaline (epinephrine) — stimulate sympathetic stress response ↑HR

↳ noradrenaline (norepinephrine) — ↑blood sugar ↑HR, BP

↳ cortisol (glucocorticoids)

↳ aldosterone (mineralocorticoids)

↳ androgen precursors

Pathobiology of the adrenal glands:

Hypofunction: destruction of the gland / insufficient stimulation → adrenal insufficiency (Addison's disease)

Hyperfunction: excessive production of a hormone / excessive stimulation of the gland

↳ The excess production may also arise from a benign tumour; adenoma

Malignant tumours of the adrenals do occur, but very rare

↓

Primary hyperaldosteronism

Phaeochromocytoma

Congenital adrenal hyperplasia

Congenital lipoid adrenal hyperplasia

Cushing's syndrome

Nelson's syndrome

11β-hydroxysteroid dehydrogenase deficiency

Neuroblastoma

Adrenocortical carcinoma

Androgen-secreting tumours

Incidentalomas

Specific Actions of Adrenaline:

1) Airways: dilation of smooth muscle
↓
Faster movement of air in and out of lungs

Spleen → increase RBC number

2) Contraction of radial & relaxation of ciliary muscles of eye → broadening & brighter field of vision

3) CNS: increased excitability & alertness

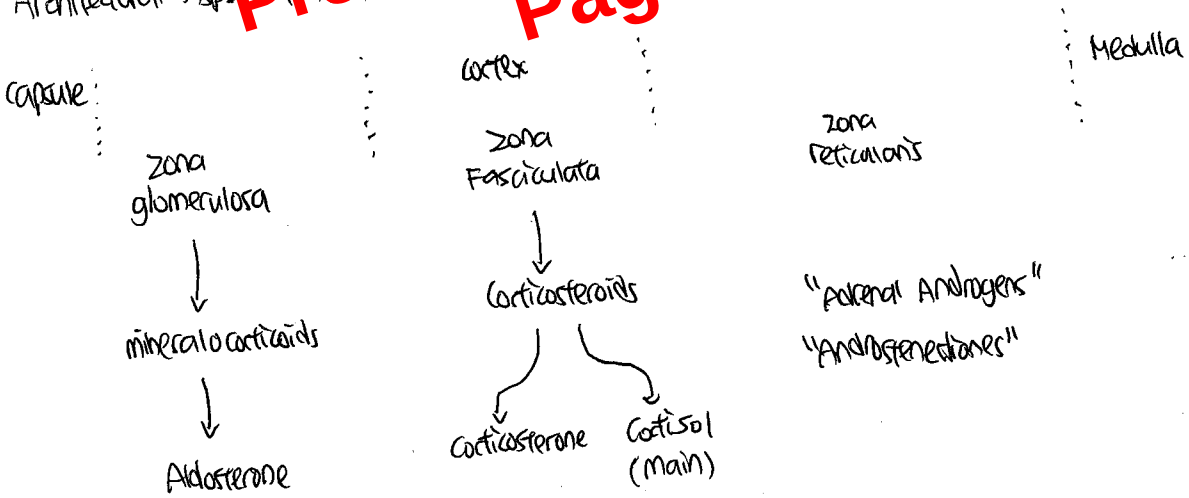
4) increased sweat production

Adrenal Medulla — ~~Pheo~~ Pheochromocytomas
↳ Tumour of the adrenal medulla which produce excess adrenaline
↳ generally benign (not likely to ~~mass~~ metastasize)

Symptoms: severe headaches, excessive sweating (generalized), racing heart (tachycardia & palpitations)
anxiety / nervousness (feelings of impending death) nervous shaking (~~the~~ tremor)
pain in the lower chest / upper abdomen, nausea, ~~weight~~ loss, heart intolerance

Treatment: Adrenalectomy (surgery)

Architectural Aspects of the Adrenal Cortex (structural organization)



Steroidogenesis: Zona Glomerulosa

↳ does NOT contain enzyme for glucocorticoid production

Cholesterol

Pregnenolone Synthase (P450scc (CYP11A1))

Regulated by ACTH

Pregnenolone [prohormone]

↳ cleavage of 6C side chain of cholesterol

↘ 3βHSD — 3β-Hydroxysteroid dehydrogenase (C3β-HSD)

↘ Progesterone

↓ P450 c21 | 21-hydroxylase CYP 21

~~11-Deoxy~~

11-Deoxycorticosterone

↓ ~~P450~~ P450 c18 | 18-hydroxylase CYP 11B2

Corticosterone

↓

18-hydroxycorticosterone

↓

Aldosterone

Aldosterone Synthase

- P450 – mitochondrial ~~enzyme~~ location
- ACTH – stimulator of steroidogenesis, key regulator of steroidogenesis
- cholesterol is transported to the mitochondria
- ~~StAR~~ & CYP 11A1 (pregnenolone synthase) is the rate limiting enzyme
- intermediates are shuttled between the mitochondria and ER
- 3βHSD steer steroid precursors away from androgen precursor biosynthesis
- In man, CYP17 prevents aldosterone biosynthesis and commits to cortisol and androgen precursor biosynthesis
- gene defects in the enzymes of biosynthesis: congenital adrenal hyperplasia

Endocrinopathies

Hypofunction : destruction of gland / insufficient stimulation → Adrenal insufficiency
Addison's Disease (subset) [not all Addison's disease is associated with adrenal insufficiency]

Hypofunction : excessive production of a hormone or excessive stimulation of the gland

Excess production may arise from a benign tumour, adenoma. Malignant tumours of the adrenals do occur, but pretty rarely.

- primary hyperaldosteronism
- phaeochromocytoma
- congenital adrenal hyperplasia
- congenital lipoid adrenal hyperplasia
- Cushing's syndrome
- Nelson's syndrome
- 11B-hydroxysteroid dehydrogenase deficiency
- Neuroblastoma
- Adrenocortical Carcinoma
- Androgen-secreting tumours
- Incidentalomas

Hypofunction : Primary Adrenal Insufficiency (Addison's Disease)

↳ symptoms relate to the degree of loss of adrenal function
these include dehydration, shock, nausea, abdominal pain, fatigue, confusion, hypotension, anorexia, vomiting, weakness, lethargy; hyperpigmentation in the oral cavity

↳ primary disease - Addison's disease, caused by damage / dysfunction of adrenal glands

↳ characterized by a decrease and / loss in both mineralocorticoid & glucocorticoids

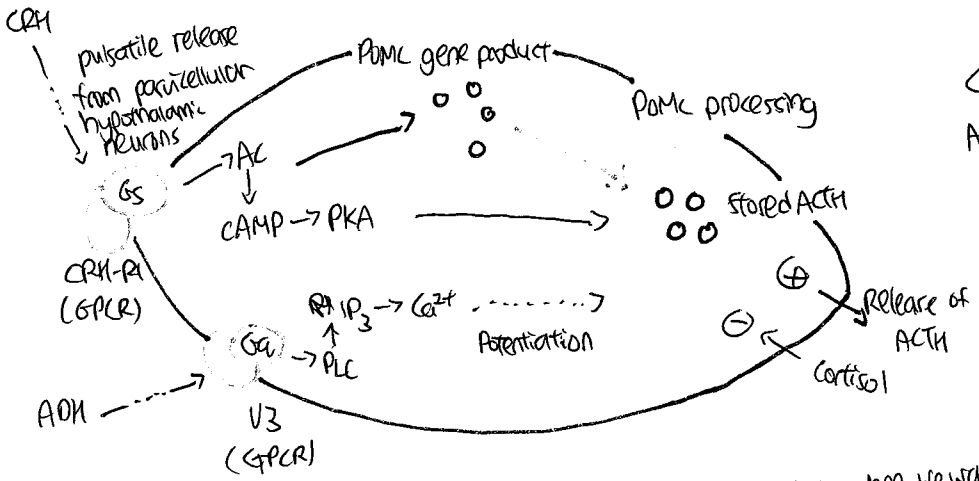
↳ untreated condition is fatal within 1-2 weeks

↳ In 2° / 3° disease, the aldosterone levels are virtually normal as Addison's disease arises from defects at the pituitary gland / hypothalamus axis (less severe)

↳ caused by : high expression levels of 11BHSD-1 (converts cortisone → cortisol)
surgical removal of glands, autoimmune disease (Addisons disease 80% of cases)
granulomatous disease (tuberculosis), metastatic malignancies, pharmacological steroid therapy, haemorrhage, meningococcal septicaemia ... etc

↳ treated by : replacement therapy for life, hydrocortisone (prednisolone / dexamethasone) for cortisol
~~fluid~~ fludrocortisone for aldosterone.

ACTH synthesis and release from pituitary corticotropes

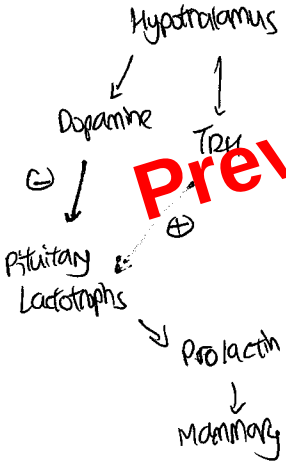


CRH - 41 aa
ACTH - 39 aa

Diurnal ACTH / CRH / cortisol release ~ the highest diff moments during when we wake up

- diurnal control mediated via suprachiasmatic nucleus (SCN) of anterior hypothalamus
- endogenous clock genes in many peripheral tissues
- retrained by light / dark cycles — peak in early morning and a valley in late afternoon
- sensitivity of tissues to hormones

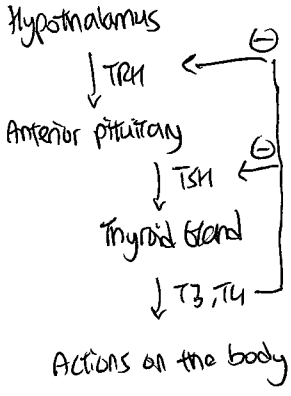
Control of PRL secretion from pituitary lactotropes



- no endocrine axis (...)
- tonic inhibition via dopamine
- puerperal breast development
- ... and maintain lactation
- sucking — neural reflex triggers PRL release

Control of TSH secretion from pituitary thyrotropes

↗ action on TRH receptor
TRH (Gq - PLC)



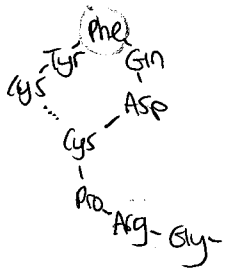
~~important pan~~

- diurnal release (↑ overnight) ↗ highest during overnight hours, lowest around 9/10am time
- stresses ↓ release
  - ↳ mental
  - ↳ physical
  - ↳ starvation
  - ↳ infection

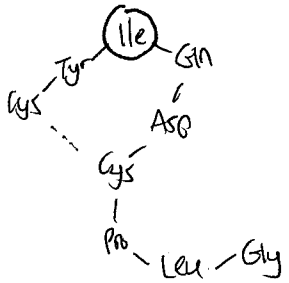
Posterior Pituitary Hormones < oxytocin
ADH (vasopressin, arginine vasopressin, AVP)

- 9 aa peptides that are synthesised in the hypothalamus and transported down axons of the posterior pituitary for secretion into blood

oxytocin differs from vasopressin in 2 of the 9 amino acids



Vasopressin



Oxytocin

oxytocin – destroyed in liver & kidney
- $t_{1/2}$ = 3-5 minutes

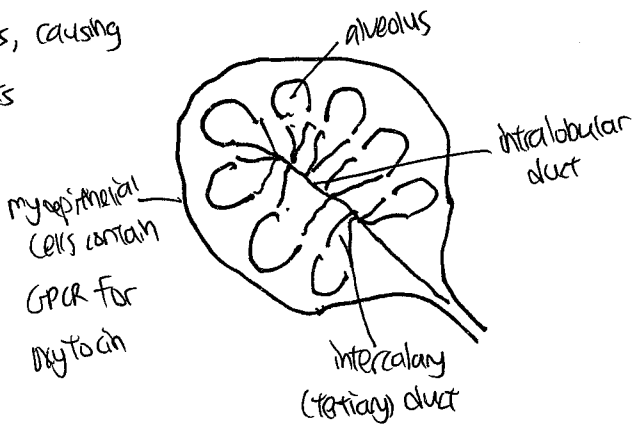
Hypothalamic control of the posterior pituitary gland
- within the hypothalamus
  - ↳ synthesis of oxytocin — para supraoptic nuclei
  - ↳ " vasopressin — paraventricular nuclei

- Both hormones packaged into granules as large precursor molecules, and transported to the posterior pituitary in combination with "carrier proteins" — neurophysins

Receptor-mediated actions of oxytocin
- via GPCR cell-surface receptors
- increase in P_i turnover
- Mobilisation of intracellular Ca^{2+} (phospholipase C pathway)
  - ↳ bind to calmodulin for further 2° responses

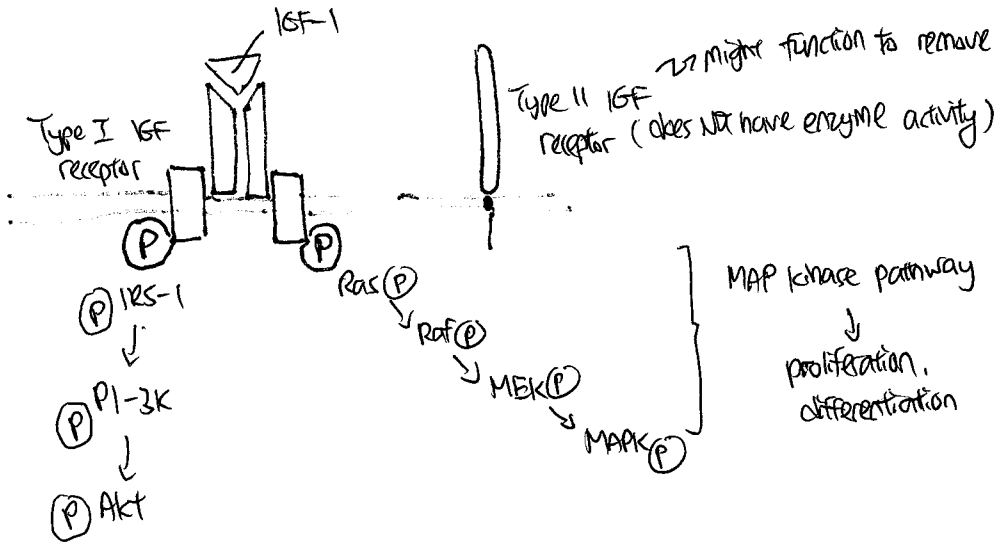
physiological effects of oxytocin
- stimulation of milk ejection
- stimulation of uterine smooth muscles contraction at birth
- Establishment of maternal behaviour

Stimulation of milk ejection
↳ within mammary gland, milk is initially secreted into small sacs called lobules / alveoli, from which it must be ejected for consumption
↳ groups of alveoli are surrounded by smooth muscle (myoepithelial) cells which are prominent target for oxytocin
↳ oxytocin stimulates contraction of myoepithelial cells, causing milk to be ejected into the surrounding ducts



Insulin-like Growth Factor-1 Axis

IGF-1 binds to IGF-R - leading to autophosphorylation



PI-3 kinase pathway
↓
survival metabolism

IGF binding proteins (IGFBP)

↝ majority of IGF is associated with IGFBP

- 6 well characterised
- evolutionary homology
- some structural similarities
- differing regulation } tissue sources

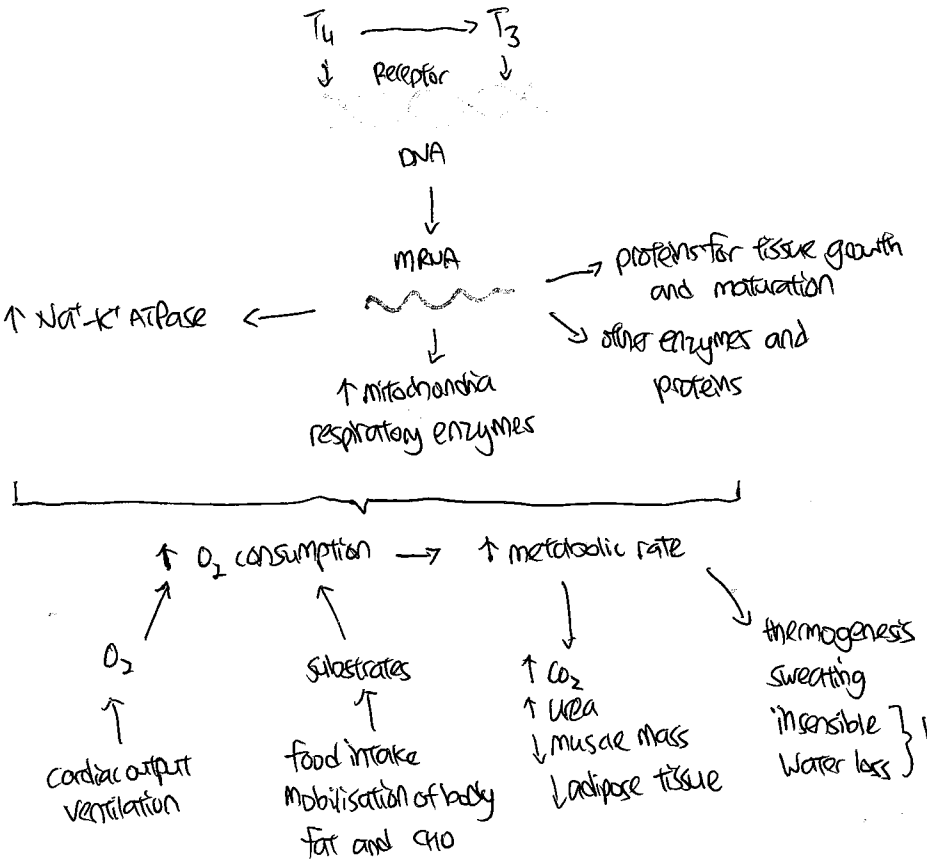
↝ IGFBP-3 main IGFBP in circulation - storage of IGF
↝ prolong IGF half life
↝ transport molecules
↝ modify IGF action

IGFBP regulate IGF activity - IGFBP has ↑ affinity to IGF than IGF Receptor
- protease can cleave IGFBP into fragments, allowing IGF to bind to its receptor

acid-labile subunit (ALS) 90kDa
needed to maintain the IGFBP-3 - IGF complex
Total size = 150 kDa

Biological Actions of Thyroid Hormones

1) Control of basal metabolic rate



Hyperthyroidism thus lead to high metabolic rate, tremor, muscle wastage, weight loss despite normal / increased appetite

↳ most common disorder in cats endocrine

2) Growth-regulating roles of thyroid hormones in adults

- most bodily functions affected
- often synergise with other hormones eg to GH in early growth & development
- deficiencies lead to abnormal growth, development, reproduction, behaviour, metabolism
- exert effects on all organs and tissues throughout life

Absence of thyroid hormones in adults lead to growth retardation

↝ arrest in bone elongation and retarded bone maturation

↝ reduction in growth hormone secretion

↝ 2-fold role of thyroid hormones — production of GH
— direct systemic actions

Estrogens in Males

- androgens are converted to oestrogen by the enzyme aromatase
- only 25% of oestrogen from testes (Sertoli cells)
- In mice, required for i) fertility - mice lacking aromatase / oestrogen receptor have impaired spermatogenesis

ii) bone mineralisation

- In humans: oestrogen receptor & aromatase mutation reported
  - ↳ reduced sperm number and motility
  - ↳ tall stature, delayed bone maturation, osteoporosis
  - : Excess leads to ~~gynecomastia~~ gynaecomastia

Male ~~also~~ menopause (andropause / androgen insensitivity)

- Total testosterone levels show modest variation w age
- sex hormone binding globulin decreases
- free androgen decreases
- Symptoms: tiredness, depression, hot flushes, sweating, decreased libido, erectile dysfunction
- replacement therapy: reduction in symptoms not very impressive
- testosterone therapy may be associated w gynaecomastia
  - aggression
  - prostate cancer
- serum LH and FSH increases

Kallmann syndrome type I: caused by failure of GnRH neurons to migrate from nasal placode to the mediobasal hypothalamus

- hypogonadotropic hypogonadism
- associated with anosmia / hyposmia (absent / poor sense of smell)
- X-linked disease, loss of functional protein, anosmin
- males suffer from undescended testis (cryptorchism), impaired LH secretion, delayed puberty

Deficient 5α-reductase could lead to ambiguous genitalia due to decreased DHT secretion

Normal human thyroid follicular cells in monolayer culture
↳ cells retain an intact adenylate cyclase
↳ response to TSH which generate cAMP
↳ in proportion to the applied TSH dose

Bioassay end point = accumulation of cAMP in human thyroid cell monolayers

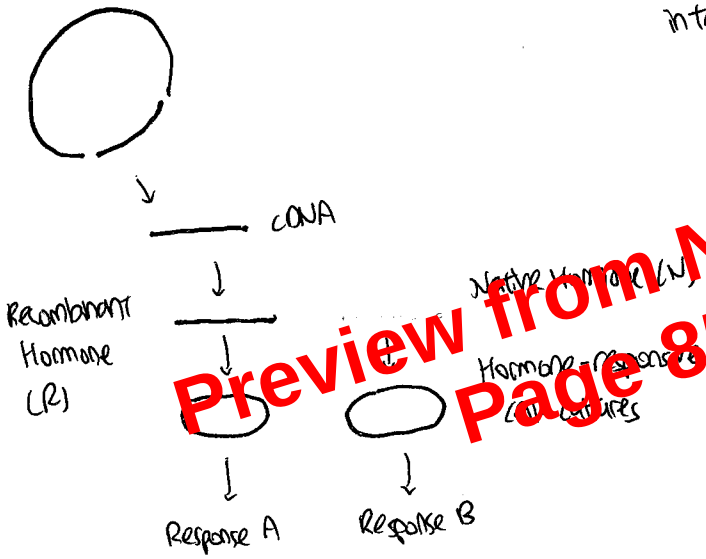
Bioassay : Limitation and advantages
In vivo bioassays : laborious, technically - demanding, expensive, insensitive
poorly reproducible, subject to species-specificity limitations

In vitro bioassays : cost-effective, robust, reliable, sensitive, precise, reproducible,
easier to avoid species-specificity problems

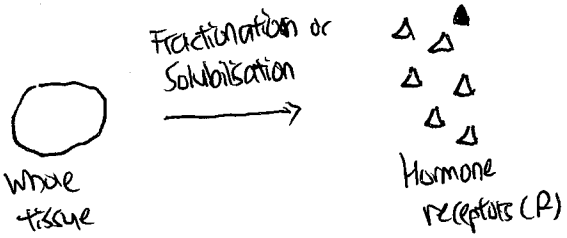
* NOT every target tissue of human available in a cell line

Assignment of potency to recombinant hormones

Calibration of R in terms of N (units of activity) and in terms of mass used (R= 100% pure)



Receptor Assays (Ligand binding Assay) ~> quite similar to radioimmunoassay
~> NOT used routinely in clinical settings



↳ can be stored in fridge over several months

$\Delta + H \rightleftharpoons \Delta\text{-}H$ at equilibrium

$\Delta\text{-}H + H^* \rightleftharpoons \Delta\text{-}H^* + H$

Competitive binding

Endocrinology of pregnancy

Role of placenta - interface between maternal & fetal plasma
- protects fetus from attack by maternal immune system
- hormone production : human chorionic gonadotrophin (hCG)
human placental lactogen (hPL)
placental growth hormone (pGH)
progesterone
oestrogen
} peptide hormones that are pregnancy-specific, produced only by placenta

- human chorionic gonadotrophins (hCG)
↳ glycoprotein hormone
↳ structurally related to LH
↳ produced by placenta (2-cell model) { GnRH produced by cytotrophoblast (inner layer of villus)
, stimulates hCG production by syncytiotrophoblast (outer most layer of villus)
GnRH
↳ produces majority of hCG, hPL, pGH
↳ signals conception to maternal organism ↗ presence of embryo
- rescues corpus luteum
- continued secretion of progesterone by ovary & therefore endometrial lining is maintained
↳ rapid increase in hCG causes morning sickness during early pregnancy

↳ detectable in maternal serum after implantation (14 hours)
↳ maintains progesterone production by placenta
↳ stimulates steroid production by fetal ~~gonads~~ placenta
hCG can be measured as a level of foetal well being
- levels double every ~~2 weeks~~ 2 days till ~~12th~~ 6th week
- if level ↑, → multiple pregnancy
- if level ↓ → ectopic pregnancy
- levels peak at 10th week

Progesterone
- produced by syncytiotrophoblast (9th week)
- dependent on maternal ~~chromosome~~ cholesterol - placenta lacks enzyme to produce cholesterol from acetate
cholesterol transported into ~~syncytiotrophoblast & mitochondria~~

- regulated by hCG
- large amounts secreted into maternal bloodstream
↳ maintains decidual lining of uterus
↳ decreases ~~PG~~ prostaglandins formation - relaxes myometrium ↗ to prevent parturition labour during pregnancy
↳ suppresses T-cells-mediated tissue rejection
↳ peripheral effects on vascular smooth muscle & other organs
↳ reason why some pregnant women experience constipation

in cases of miscarriage, levels of progesterone found to be low (< 10 ng/ml)
↓
80% miscarriage

- progesterone production does not depend on foetal well being, can't be used as a marker for foetal growth

Fetal Endocrinology

- Most hormones have similar function in adults and foetus
  - ↳ exceptions: T_3 and T_4
    adrenal hormones
    GH

Thyroid Hormones

Fetus - T_4 from week 18
- T_3 low due to low D1o1 (liver)
  high D1o3 (placenta)

preferential production of rT_3

T_3: important for foetal brain development. Brain has enzyme needed for $T_4 \rightarrow T_3$

At birth - TSH, T_3 & T_4 rise rapidly (↑ most probably because of the cold)
- adult levels achieved within a few weeks

Adrenal Hormones

- glands disproportionally large in foetal life due to fetal zone of cortex
- fetal zone produces DHEA
- medulla - initially noradrenaline
  - ↑ at parturition
  - neonate function - thermogenesis
    - surfactant release (↑ pulmonary function)
    - blood pressure

Growth Hormone:

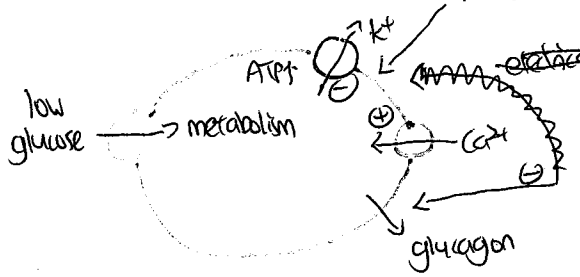
Fetus: controlled by
- genetic factors
- placental function - nutrient uptake
  - hormone production eg: placental GH & placental lactogen

- IGFs
- Human IGF-1 knockout → low birth weight
- IGF-1 levels: decreased in fetal growth restriction
  Increased in Large-for-Gestational-Age

Neonate: GH receptors increase
: IGF responsive to pituitary GH

Glucose-sensing by α-cells and Glucagon Secretion

limited no. of secretory granules in α-cell → transient insulin release



In high glucose, there is electrical inactivation
↳ depolarises in a level that Ca2+ channels cannot open

In high glucose, there is electrical inactivation.

glucose-induced inhibition of glucose secretion

Same molecular sensing apparatus as β-cells, BUT diff. functional responses at diff. [glucose]

↳ In some hyperglycaemic cases, α-cells does NOT switch off glucagon production

Diabetes Mellitus

- a chronic disease, which occurs when the islets of Langerhans do NOT produce enough insulin, or when body cannot effectively use the insulin it produces — leading to hyperglycaemia

T1DM → insulin dependent, characterized by a lack of insulin production

T2DM → non-insulin dependent is caused by either / both defects in glucose sensing by islets and of insulin signalling

Endocrine Treatment for T1DM

- insulin administration
- islet transplantation
- stem cells — produce insulin-producing stem cells → stimulate embryonic stem cells to differentiate into insulin-producing stem cells using different growth factors & transcription factors

adaptation of body's physiological system only exist in T2DM not in T1DM

T2DM treatment options

- reversal through lifestyle changes
- bariatric surgery for cure of diabetes