Systems of the Body 3

Endocrine and Reproductive Systems

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Lecture 3: Organization of the Hypothalamus and Pituitary Glands

The hypothalamus surrounds the third ventricle and is connected to the pituitary via a stalk. The anterior and posterior pituitary are distinct in their tissue types. There is portal blood vessels in and on the structures. The Hypothalamo-pituitary axis is the interface between the CNS and endocrine system. It is used for numerous functions such as reproduction and energy balance.

The pituitary stalk is delicate and passes through a layer of dura over the sinus, in the sphenoid bone, in which the gland sits. Serious head trauma can rupture the stalk severing the connection between the hypothalamus and the pituitary. The fossa the gland sits in is the sella turcica. The pituitary is near the optic chiasm and tumours are common. Since it can’t grow down due to the sphenoid bone they grow up and hit the optic chiasm and thus visual disturbances are a common sign.

The hypothalamus is part of the diencephalon on either side of the 3rd ventricle. The bottom part of the hypothalamus is called the median eminence. The tuber cinereum is the connecting stalk. The hypothalamus is arranged in nuclei. Each nuclei makes distinct hormones; although hormones can be made in multiple nuclei. Such as the paraventricular and supraoptic nuclei which both make oxytocin. The nuclei house the cell bodies. There are 3 zones of cell bodies; periventricular (near the ventricle), medial and lateral. Endocrine nuclei are found in the medial and periventricular zones. Note: the median eminence has no cell bodies.

The hypothalamus has neurosecretory cells. These transduce action potentials into endocrine signals. The peptides are made in the cell bodies, hence the large cell bodies as they house the synthetic machinery, then taken to the axon terminals. Note there is synchrony of firing of nerves in the nuclei such that pulses of hormone release are seen rather than drips and drabs. Naturally rate of release depends on firing of action potentials and the rate of synthesis.

There are both descending (from higher brain centres) and ascending (e.g. from the gut) inputs into the hypothalamus.

Circumventricular organs- these lie around the ventricles; on the midline of the 3rd and 4th. Here the blood brain barrier is reduced- thus are a route for large molecules into the brain. Have roles in fever and appetite. Median eminence is considered one of these organs. The neurons here connect to the hypothalamic nuclei to modulate its function.

Embryological Development
Lecture 4: Hypothalamic Regulation of the Pituitary

There are 3 main groups of hormones made in the anterior pituitary gland:
- Corticotrophin related peptides
- Glycoproteins
- Somatomammotrophins

**Corticotrophin Related Peptides**

These are small peptides derived from a common precursor: POMC. The main hormones are ACTH, alpha melanocyte stimulating hormone, B-lipocortin and beta endorphin. The POMC is cleaved in different sites along the protein to give the different peptides depending on the site of synthesis in the brain. ACTH in the intermediate lobe can be cleaved again to form alpha-MSH and CLIP.

**Glycoproteins**

These are comprised of an alpha (which is constant in all hormones) and b subunit (this varies from hormone to hormone and so gives the specificity). Hormones are glycosylated and then secreted. The addition of carbohydrates and sialic acid increases the half life; those with the most additions are the most stable. Examples include follicle stimulating hormone (FSH), luteinizing hormone (LH) and Thryotrophin (TSH). Note the hormones are only active when the alpha and beta subunits are joined together.

**Somatomammotrophin Hormones**

These are single peptide chains with 2 or 3 disulphide bonds; with no carbohydrate groups. Include prolactin (PRL) and growth hormone (GH or somatotrophin).

**Hypothalamic Hormones**

**Neurohypophysial Hormones (Posterior Pituitary)**

Remember the magnocellular neurons project to the posterior pituitary where hormones are released. These hormones as vasopressin (or ADH) and oxytocin (OT). Both are synthesized in the supranoptic and periventricular nuclei and are nonapeptides. They have a similar structure of 9 amino acids.

ADH acts to cause antidiuersis and control arterial blood pressure. Defects lead to diabetes insipidius.

OT- causes milk ejection and expels fetus at parturition (head of child on cervix causes releases of OT which stimulates contraction).

Remember these cells also have projections to the brain and so can modulate behaviour; for example, oxytocin release is used to initiate maternal behaviour.
Hypophisiotropic Hormones (Anterior Pituitary)

Hormones are transported to the median eminence and released into the portal circulation where they control the anterior pituitary function. Lots of examples:

- **CRH** (corticotrophin releasing hormone). Made in paraventricular nucleus. Stimulates synthesis and release of ACTH from pituitary corticotroph cells.
- **TRH** (Thyrotrophin releasing hormone)- made in pareventricular nucleus. Stimulates synthesis and release of TSH from pituitary thyrotroph cells. Also, in high amounts, causes the release of prolactin.
- **GnRH** (Gonadotrohin Releasing Hormone)- made in arcuate nucleus. Stimulates synthesis and release of LH and FSH from pituitary gonadotroph cells.
- **GHRH** (Growth Hormones Releasing Hormone)- arcuate nucleus. Stimulates synthesis and release of GH from pituitary somatotroph cells.
- **Somatostatin (SS)**- periventricular nucleus. Inhibits synthesis and release of GH—growth hormone is special as it has an agonist and antagonist releasing hormone. Also acts to inhibit TSH release.
- **DA** (Prolactin Inhibiting Hormone or Dopamine as it was later found to be)- made in the arcuate nucleus. TIDA neurons are dopamine neurons that project to the median eminence. This is a monoamine hormone. Inhibits the release of PRL from lactotroph cells of the pituitary.

Regulation of the Hypothalamo-Pituitary Axis

Lots of detection of stimuli routes e.g. CSF or neural inputs. Neuronal signals are transduced to hormonal ones. There is gross amplification of the signal as we move from the hypothalamus, to pituitary and out to the periphery. There is then mainly negative feedback- i.e. once the hormone is released, it feeds back to inhibit release of the hormone again.

Individual Control

ACTH leads to the release of cortisol from the adrenal glands which is key for managing stress. AVP is vasopressin and this acts to potentiate ACTH release. Cortisol is released from the cortex of the adrenal gland. Under use of this pathways gives us Addison’s Disease (hypotension, hypoglycemia and hyperkalemia- often with pigments in the oral cavity). Coristol acts as a negative regulator of this loop. ACTH release is highest when we wake up and lowest at midnight. Stress activates this pathway.
Remember TRH acts from the hypothalamus onto the anterior pituitary to release TSH and thus cause release of thyroid hormones. TSH is a useful marker for thyroid function as it is very sensitive to thyroid function. TSH and T4 have an inverse linear relationship [low T4 means high TSH and visa versa] although this only holds true in stable thyroid function states.

**Goitre**

This is enlargement of the thyroid. Can occur in hypo and hyper states; for example iodine thyroid deficiency we see a growth of the thyroid to try and compensate for the lack of iodide. This condition is a global problem with 30% of the worlds population at risk; especially land locked regions. In the UK the most common cause is **Hashimoto's thyroiditis** which is an autoimmune hypothyroid condition.

**Hypothyroidism**

Symptoms present early in development with cretinism: neurological deficits, small stature with immature appearance, puffy hands and face and delayed puberty (are infertile). Thus we screen neonates for TSH and T4.

In adulthood we have insidious onset with low BMR and cold sensitivity, bradycardia, slow hoarse speech, weight gain, constipation and myxedema (dry thickened skin) amongst many other signs.

Causes: Hashimotos – an autoimmune condition where antibodies are made against thyroglobulin or thyroid tissue. Thyroid radiation, HPA deficits or iodide deficiency.

To treat we replace T4 dosage can be hard to get right.

**Hyperthyroidism**

Thyrotoxicosis – to much activity. Gives effects such as restlessness, tremor, tachycardia, high BMR, increased appetite with weight loss and tiredness. Most common is **Graves disease**. This disease has characteristic eye signs – exophthalmos- where eyes stick out.

Other causes include toxic multinuclear goitre, toxic adenoma and pituitary tumors. Note these don’t have the eye problems.

Treatment involves antithyroid drugs:
- Carimazole and propylthiouracil which stop the T4-T3 conversion.
- Propranolol – for blocking the effects the hormones have on the B adrenoreceptors e.g. tachycardia.

We may also give radioactive iodine to kill the thyroid and surgery- although these risk inducing hypo conditions.
Oocytes are arrested in prophase 1 of meiosis 1. Primordial follicles form a pool around the edge of the cortex.

**Follicular Atresia:** this is essentially programmed cell death. Follicular atresia is the major reason for loss of follicles. Occurs at all stages but greatest lost is in primordial and primary follicle stage. Much occurs before birth and continues through childhood so by puberty there are about 0.5 million follicles remaining. Atresia is not altered by pregnancy or being on the pill. Atresia can be accelerated by genetic disorders, and chemotherapy. A woman only needs some 460 eggs for her menstrual life.

### Primary Follicle

The formation of this is independent of LH and FSH. Formation is independent of LH and FSH. Involves:
- Enlargement of oocyte (still in arrested meiosis)
- Proliferation of granulosa cells
- Formation of theca interna
- Formation of zona pellucida
- Zona pellucida is 5mm thick glycoprotein (important in fertilisation and early cleavage). Zone pellucida stops multiple sperm fertilising the egg. Lack of this leads to non-fertilisation.

Activins & AMH involved in growth. Most primary follicles undergo atresia.

### Secondary Follicle

This requires the HPO axis to be switched on- allows the female to grow follicles rapidly. There is secretion of follicular fluid into the antrum which will concentrate hormones that are made. The antrum fluid is made by the granulosa cells.

The follicle will produce Oestradiol 17b which is stored in the antrum- allowing the follicle to auto regulate its own growth.

Secondary follicles are also called antral follicles. Has a fluid-filled antrum. Formation needs both LH and FSH. Slight rise of FSH causes approx 12 of these to form at start of each menstrual cycle. Formation involves:
- Further proliferation of granulosa cells
- Formation of antrum
- Activation of theca interna

Produce **Oestradiol.** Most undergo atresia. Activation of the theca interna- the outer layer of cells outside the BM of granulosa cells are activated by LH/FSH and make this Oestradiol.

Production of steroids:
presentations. Dizygotic have two sacs. We label the twins on if they have a shared or single placenta and a shared of single sac. Sharing a sac is a risk for still birth as the chord gets tangled.

From 7 weeks we can see on ultrasound a small bean like structure. At 11 weeks we see a foot.

**Beta HcG**

Glycoprotein of alpha and beta subunit that is produced by Trophoblasts. Used for pregnancy testing. Used to maintain progesterone and oestrogen in early pregnancy. Falls after 12 weeks.

**False Negative**
- Wrong timing- trophoblasts start working at 5-6 days but need a rise in the serum. Conceive at usually day 15/16.
- Assay only detects biologically active hCG

**False Positive**
- Liver disease
- Have to read after the set time.
- Gestational Trophoblastic diseases
- Germ cell tumours
- Ig A deficiency
- Evaporation line / left test too long

**Changes in Early Pregnancy:**

Progesterone is the driving force behind the changes in early pregnancy. Most things in the blood increase. Learn the % increase. In early pregnancy the mothers blood volume rises by 30%, plasma volume by 50%, RBC mass by 25% [so a physiological anemia is normal in pregnancy because we dilute the red blood cells] and cardiac output but 30-40% with increases in HR to. We see a fall in peripheral resistance- progesterone causes a massive fall in peripheral resistance to allow the heart to cope with these changes. It declines until the second trimester and will begin to rise again back to normal level by due date.

**Respiratory changes:**

Increases:

- Minute volume (50% by 2\textsuperscript{nd} Trimester)
- Tidal volume (40%)
- Respiratory rate (15%)
- Alveolar ventilation (70%) as dead space remains unchanged
- Sensation of breathlessness (Progesterone)

You have dyspneoa sometimes.

Decreases:
Airway resistance (Progesterone)
Total lung capacity
  • Flaring of ribs
  • Upwards elevation of diaphragm
  • Increase in diameter of chest

Renal

Relaxation of the smooth muscle (increase in UTI). Renal blood flow increases in the 6th week. Increase in renal renin (balances the rise in sodium that is causes by increased clearance and natriuretic affect of progesterone). GRF increases by 60%. Urea, creatinine, LFTs lower reference ranges. Expect creatinine to be about 60- lower than normal people.

GI

Relaxation of Oesophageal sphincter (acid reflux). Gastric secretion reduced. Gastric stasis. Reduced intestinal motility (constipation but greater absorption of nutrients). Again due to progesterone.
Lecture 21: Placenta

Development of the Placenta:

- Invasion of the endometrium and implantation
- Formation of lacunae in syncytiotrophoblast
- Formation of primary villi
- Formation of secondary villi, tertiary villi and cytotrophoblastic shell
- Branching villi
- Differentiation of chorion laeve and chorion frondosum
- Final structure of placenta
- Changes in placental barrier through pregnancy. The maternal and fetal circulation don’t actually come in direct contact- the placenta will help this. The villus is fetal and the lucana is maternal; there is a barrier which allows nutrient transfer.
- Invasion and erosion of spiral arteries

Implantation: The process by which an embryo attaches to the uterine wall and penetrates the circulatory system of the mother to form the placenta. Begins 2-3 days after the embryo enters the uterus and is limited by time and space. Timing is hormonal dependent. Cleavage occurs to isthmus. As it is in cavity of uterus it is the blastocyst. Implantation is invasive; the whole blastocyst enters the endometrium and is completely embedded.

Implantation begins with apposition and adhesion of the blastocyst to the uterine epithelium, about 2-4 days after the morula enters the uterine cavity. Mediated by cytokines and involves adhesion molecules (integrins) that interact with extracellular components, especially laminin and fibronectin. In clinical settings we tests these proteins to help determine the risk of premature labour.

Trophoblastic invasion rapidly follows adhesion of the blastocyst, mediated by proteinase degradation of the extracellular matrix. The placenta is formed in the second week after ovulation. Limitation of trophoblastic invasion is due to restraint imposed by proteinase
STIs can cause ectopic pregnancies; chlyrmdia is biggest cause of tubular infertility.

STIs can cause infertility, cancer, pain and psychological damage.

**Bacterial**
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- Bacterial vaginosis

**Viral**
- HIV
- Genital Warts (HPV)
- Molluscum contagiosum
- Genital Herpes
- Hepatitis B

**Parasitic**
- Pubic lice
- Scabies

**Fungal**
- Candidiasis

A lot of stigma with STI’s.

Sexually active: new partner in past 3 month.

No normal sexual behaviour so we do number of others.

Once per week is average. MSM and FSF increasing.

Most partner change in Black African; lowest in Indian and Pakistani populations.

MSM: unprotected anal intercourse huge risk.

STI’s are mainly asymptomatic especially in women.

**Particularly effect:**
- Young
- Men who sex with men
- Black African/Caribbean
- Inner cities
- Middle youth?

Gonorrhea occurs in outbreaks and tends to affect MSM who have sex later. Men have loads of syphilis (MSM mainly) and females don’t tend to see this.

Why have STI’s increased?

Increase in duration of “sexual careers”:
adult phase the amplitude falls but there is still more than before puberty. So pulsatility increases. This follows increases in pulsatility of GnRH.

Mechanism of Puberty

Need to reactivate GnRH. The endogenous stimulation of GnRH release is the rate-limiting step for puberty. Restraint on GnRH secretion must be removed. Some theories:

- The GnRH system becomes less sensitive to hormonal theory. The gonadostat.
- Pineal hypothesis. Thought that elevated melatonin suppress GnRH. Less favoured.
- Somatometer hypothesis. This is to do with leptin. This is accepeted. The body weight is key for stimulating puberty. Relationship between body weight and onset of puberty in girls has remained constant for more than 100 years. Critical weight is 47kg for females to go through puberty. Leptin does this signalling. Thought to have a role in the hypothalamus to reactivate the GnRH with kisspeptins. Boys seem to be about 55kg.

Disorders

Precocious puberty

- Puberty before 7 years in girls/ 8 years in boys is regarded as precocious
- May be GnRH dependent or GnRH independent.
- Can result from endocrine cause or tumour

Delayed puberty

- Puberty not achieved by 17 years
- May be hypergonadotrophic delayed puberty- excess isn’t coupled with gonad.
- May be hypogonadotrophic delayed puberty- example Prader Wili syndrome.
  Metabolic disorder. Makes you fat.

Hyperprolactinemia can suppress GnRH.
**Reduced effect of Progesterone** (removal of collagenase inhibition in uterus (and also cervix?)

**Relaxin** (increases collagenase activity)

**Nitric oxide**

**Apoptosis** (cervical ripening tends to occur spontaneously)

Toward term we have a softened cervix and fully effaced. The mother placenta and fetus have a role in initiating labor. **CRH is a peptide hormone, hypothalamic releasing factor, secreted by placental trophoblasts.** Maternal plasma CRH levels rise during pregnancy (elevated plasma CRH levels have been associated with preterm labour). CRH receptors are present in the myometrium and fetal membrane. CRH is secreted by placental trophoblasts. Three weeks before the onset of spontaneous labour:

- Rise in plasma CRH concentrations
- Abrupt fall in CRH-BP (blocks bio-availability of CRH) concentrations in the maternal circulation and amniotic fluid. Binding proteins make a reservoir of active substances; i.e. not active at time but can be activated if needed.

Placenta can secrete CRH! The CRH has numerous roles:

- Stimulates the release of prostanoids from human amnion and decidua
- Potentiates the action of oxytocin (stimulating uterine contractions)
- Potentiates prostaglandin F2a (stimulating myometrial contractions) - this is key in labour.
- Induces synthesis of prostaglandins and glucocorticoids, which feedback to increase CRH so its positive feedback.

**Fetal Role**

Baby has full HPA axis. DHEAS is made by the baby. This is substrate for oestrogen in the placenta. This rises oestrogen and DHEAS. E3 is placenta. E1 is menopause.


Progestosterone withdrawal theory of labor. It hyperpolarizes myometrial cells; promotes NO synthesis (this is a muscle relaxant) and also suppresses CRH. We think it maintains pregnancy.

**Role in late pregnancy in initiation of labour.** Anti-progesterones will cause cervical ripening and initiate labour BUT exogenous progesterone will not prevent onset of spontaneous labour AND progesterone concentrations do not fall at term.
There are non contraceptive benefits to. Can improve their skin and bleeding patterns.

Average age of sexual intercourse is 16.

60% higher infant mortality increase in teenage pregnancy.

1967- abortion legalized.
Bony pelvis
- Damaged pelvis
- Contracted pelvis (rare)

Soft tissues
- Masses
  - Fibroid- in the uterus. If this is high up it doesn’t matter but lower ones may block the passage.
  - Ovarian cyst.
  - Placenta may be to low.

Passenger

Suboptimal position of head
- Deflexed- we like the head to be nice and tucked in.
- Rotational malposition of head- want it to face floor on delivery.
- Occipitoposterior (OP)
- Occipitotransverse (OT)

Malpresentation of head
- Brow
- Face (mentoposterior)

Abnormal presentation
- Shoulder

Size of fetus: Cephalopelvic disproportion (rare), CPD

So how powerful are our contractions, are there any blockages and what position is the baby in?
Examine the partogram which explains how quickly labor is progressing. Need 10cm dilation. Examine the abdomen for how much head is in the abdomen and vaginally for head position and descent.

The thinnest bit is the ischial spine. If the head is past this we know that is near the end. If they are above this we may need to a c-section rather than vaginal assisted delivery if labour is to long.

Vaginal Exam

Station (-3 to +2 to ischial spines)
- Presentation
- Position
- Signs of disproportion
  - Caput succedenum (+, ++, +++)- swelling on top of the head. Fluid builds up as it tries to get out.
  - Moulding (+(opposing), ++(overlap reducible), +++(overlap irreducible)) – how much of the bones have overlapped.
Then we need to decide where the problem is; i.e. power, passage or child?

Problems with power

**Action**
- Rehydrate
- Syntocinon
- Encourage pushing
- Consider assisted delivery
- **No longer than 3 hours in 2\textsuperscript{nd} stage (to reduce risk of pelvic floor damage).**
  This can lead to problems for the mother e.g. incontinence.

Problems with Passages

- Careful assessment (examination)
- Consider assisted delivery (forceps/ventouse) or LSCS
- If unsure consider “trial” (in theatre)- take to theatre just incase we need to change to c-section.

Problems with the baby

- Accurate assessment of position/presentation
- Consider assisted delivery (forceps/ventouse) or LSCS
- If unsure consider “trial” (in theatre)

**Forceps:** when head below the spine does not require maternal effort. Needs pudendal nerve block or epidural and empty bladder. Safer for baby than a ventouse. Need to make sure baby is in right manner.

**Ventouse:** silicone cup. Head below the spine and does require maternal effort. Local analgesia is okay. Not to painful to use. Advice baby will have some swelling on head. These are safer for mum. A full bladder could keep the baby in.

Some babies don’t look the right way so we can try and rotate them. We can use the ventouse; as we pull the muscles of the pelvis will encourage the baby to turn. You can use your hand- manual rotation. Or special forceps; ones that don’t slide- Kiellands forceps. These need a lot of training. Thought to damage baby and can tear vagina- they are used with care.

**C-section.** If the baby is to high; cant get the baby out or a pelvic tumour.