Endocrinology – general, hypothalamus, pituitary

Rudolf Cardinal, 18 Oct 98

Communication between cells: overview

Cells may communicate **mechanically** or **electrically** (via gap junctions), but most intercellular communication is **chemical.** Chemical communication may be classified as follows:

- *synaptic* – a neuron releases a neurotransmitter across a synaptic cleft to act on the postsynaptic cell.
- *paracrine* – a cell releases a chemical messenger which acts on cells in the immediate vicinity. An example is the local release of histamine in inflammation.
- *endocrine* – a cell releases a chemical messenger (hormone) into the blood, which regulates activity in distant cells
- *autocrine* – a cell releases a chemical messenger and is itself influenced
- *non-specific* – exchange of metabolites rather than specific messengers (see below)

Remember the distinction between **endocrine** and **exocrine** secretion. Some organs are both endocrine and exocrine; the pancreas and liver are the best examples.

Neurotransmitters and endocrine hormones are two of the four major classes of soluble intercellular signalling molecules: the others are *autacoids* (a pharmacological term for paracrine agents such as histamine) and *cytokines* (in some ways very much like hormones, they are non-immunoglobulin signalling proteins that are important in regulating tissue modelling and remodelling, and the immune system).

Hormones

Definition. "A hormone is a substance released *directly into the blood* by *specialized cells* in *response to a specific stimulus*, in amounts which vary with the strength of the stimulus. The substance should be present in the blood only in minute concentrations, and should exert effects on its *target cell* by regulating pre-existing cellular reactions, by means *other than the provision of metabolic energy*."

General. When you learn about a hormone, think first about its chemical characteristics, synthesis and secretion, mechanism of action, physiological effects and how it is controlled.

Know important examples within a family of hormones (e.g. glucocorticoids – think of cortisol).

Then pay attention to the detail: secretion rate, plasma levels and how/whether it is bound to plasma carrier proteins; how it is catabolised and excreted.

From a medical point of view, know the causes and effects of deficiency and excess, and the pharmacological manipulations that exist (direct agonists and antagonists, other methods of influencing the system). *Primary* excess or deficiency refers to a cause within the endocrine gland (e.g. it's diseased, or has a secreting tumour in it). *Secondary* excess or deficiency refers to causes outside the endocrine gland – typically, the systems that control secretion have gone awry.

If you can, know something of the history of the hormone –in particular the experimental evidence for its existence, function and control – and how it is assayed.

Categories of hormone. Hormones fall into **3** main categories:

- **peptides,** which are made by ribosomes and stored in exocytotic vesicles. Often they are first made as a *prohormone* (a larger peptide that is cleaved to give the hormone; sometimes the prohormone itself comes from a *preprohormone*). They are *water-soluble.* They act on *cell-surface receptors* on the target cell to influence intracellular messengers, so typically act *fast*. They are catabolised by peptidases.
- **steroids,** which are synthesised in the SER. They are *fat-soluble* and cross the plasma membrane. For this reason, they are not stored in significant quantities. Often they are bound to carrier proteins in the plasma. They act on *nuclear receptors* in the target cell to regulate *gene expression*, and their action is therefore *slow* and *long-lasting*. They are catabolised by conjugation in the liver to less active, more water-soluble forms.
- **thyroid hormones,** which are a special case: they contain *iodine* and have many features in common with steroids.

Water-soluble hormones act at three classes of cell-surface receptor:

1. Transmembrane ion channels
2. G-protein-linked receptors (either via the cAMP pathway, or the PLC→IP_3/DAG pathway)
3. Enzyme-linked cell-surface receptors (binding triggers enzymatic activity directly)

Nomenclature – caution! Many hormones have several names. I've put the commonly used ones in bold.

Endocrine glands

The endocrine glands synthesize and release specific hormones. We will examine them separately. In general, know their location, anatomy (including blood supply, especially if there is a portal system), nerve supply, histological features, non-endocrine function – and above all, which hormone they produce!

The pituitary

The master controller of many endocrine glands. Also known as the **hypophysis.**

Main division	Subdivision	Function / hormones
adenohypophysis[1] (derived from Rathke's pouch, an outpouching of ectoderm from the roof of the pharynx – grows up)	pars distalis } **anterior pituitary** pars tuberalis } pars intermediate (intermediate lobe)	opiomelanocortins: … several, including… ***adrenocorticotrophic hormone (ACTH)*** glycoproteins: ***thyroid-stimulating hormone (TSH)***[2] ***follicle-stimulating hormone (FSH)*** ***luteinizing hormone (LH)*** somatomammotrophins: ***prolactin (PRL)*** ***growth hormone (GH)***
neurohypophysis (downgrowth from the CNS – very few cells here; mostly consists of nerve terminals from cell bodies within the CNS)	pars nervosa (**posterior pituitary**) infundibulum	The nerve terminals contain neurosecretory granules. They release them into the circulation (neurosecretion). ***oxytocin*** ***antidiuretic hormone (ADH)***[3]

The pituitary sits in the **sella turcica,** just underneath the **optic chiasm**. Supplied by the anterior and posterior hypophysial arteries. The **pituitary portal system** is a set of portal capillaries from the hypothalamus to the anterior pituitary, allowing hypothalamic hormones to be delivered to the pituitary in high concentrations.

Anterior pituitary hormones

Very important. Discussed in detail in separate handouts – see also section on the hypothalamus (next page).

The opiomelanocortins are structurally very similar to each other; they are all made from the precursor pro-opiomelanocortin. They include ACTH and melanocyte-stimulating hormone (MSH). The structural similarity means that overproduction of ACTH causes skin pigmentation.

The glycoproteins also resemble each other. They are composed of an α chain (identical in all hormones) and a β chain (unique to each hormone, it confers specificity).

Posterior pituitary hormones

Oxytocin is involved in the control of milk release and uterine contraction in labour. No known function in the male. More detail in the reproduction course.

ADH is vital in the regulation of extracellular fluid volume, and you should have covered it last year.

Pituitary disease – overview

Vascular. Portal circulation $\Rightarrow$ vulnerable to hypotension (Sheehan's syndrome – enlarged pituitary in a pregnant woman is infarcted following blood loss in labour).

Neoplastic – endocrine effects. Adenomata may produce pituitary hormones ($\rightarrow$ 'secondary' excess of the hormone produced by the target endocrine gland) but also squash neighbouring cells, causing deficiency syndromes.

Neoplastic – neurological effects. Expansion of the pituitary squashes the optic chiasm, causing tunnel vision (bitemporal hemianopia).

[1] Adeno = glandular.
[2] Also known as thyrotropin.
[3] Also known as vasopressin, and arginine vasopressin (AVP)

The hypothalamus

From an endocrine point of view, the controller of the pituitary (and therefore all its target endocrine glands). Remember, though, that the hypothalamus is a key part of the nervous system and has many other roles in the control of behaviour. It is composed of many nuclei.[4] It functions in three main ways:

1. *via control of the pituitary* (puberty, ovulation, parturition, lactation, testicular function, sodium/water homeostasis, basal metabolic rate, energy metabolism, growth, circadian rhythms[5]).
2. *via control of the autonomic nervous system* (BP, cardiac output, temperature, adrenal medulla, gastric function, pancreatic function, external genitalia etc.)
3. *via control of behaviour* (eating, drinking, salt appetite, aspects of fear/flight/fight behaviour, parental and sexual behaviour, behavioural temperature regulation etc.)

Recall that the hypothalamus influences *posterior* pituitary hormones directly, by nervous signalling. In truth, most of the posterior pituitary is merely a set of neurosecreting terminals of cells that are in the hypothalamus – specifically, the supra-optic nucleus (SON) and paraventricular nucleus (PVN). *Anterior* pituitary hormones are influenced via the pituitary portal system.

These endocrine systems are best viewed as a series of **axes;** for example, the hypothalamic–pituitary–adrenal (HPA) axis, or the hypothalamic–pituitary–ovarian (HPO) axis.

hypothalamic hormone (& effect on pituitary)	**pituitary cell type / hormone**	**target gland**
corticotropin-releasing hormone (CRH) stimulates ***ADH*** stimulates	corticotroph – ***ACTH***	adrenal cortex
dopamine (DA) inhibits[6]	lactotroph – ***prolactin***	breast (i.e. direct actions on tissue)
thyrotropin-releasing hormone (TRH) stimulates ***somatostatin*** inhibits[7]	thyrotroph – ***TSH***	thyroid
growth hormone-releasing hormone (GHRH)[8] stimulates ***somatostatin*** inhibits	somatotroph – ***GH***	liver (but GH also has direct actions on tissue)
gonadotropin-releasing hormone (GnRH) stimulates	gonadotroph – ***FSH & LH***[9]	testis / ovary

Typically, the end hormone regulates hypothalamic and/or pituitary hormones for homeostatic purposes – negative feedback is the rule, though positive feedback occurs in the ovarian cycle.

[4] In neurobiology, a nucleus is a group of neuronal cell bodies (grey matter) in the CNS.

[5] Circadian = having a period of *about* a day (24 h) – *circa* about, *dies* day. When endogenous circadian rhythms are exactly entrained to the environmental day/night cycle, they are *nycthemeral*. The **suprachiasmatic nucleus (SCN)** of the hypothalamus is crucial in regulation many such rhythms; the body's "master clock".

[6] So dopamine antagonists such as the neuroleptics, used in the treatment of schizophrenia, can cause lactation – even in the male.

[7] Somatostatin inhibits secretory processes wherever it occurs – nicknamed "endocrine cyanide".

[8] Going for the prize for most confusing set of names… GHRH is also known as STH-releasing factor and somatocrinin; growth hormone (GH) itself is also known as somatotropin and somatotrophic hormone (STH); somatostatin is also known as STH-release-inhibiting-factor (SRIF). I put these in for your reference as you may come across them elsewhere; they're older names and you should ignore them.

[9] FSH and LH are known as the ***gonadotrophic hormones***. This *is* a widely-used term.