Current Diagnostic and Therapeutic Approaches in Nuclear Endocrinology

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Edited by

David Taïeb and Karel Pacak

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PART 1.

THE BASICS

CHAPTER ONE

PRINCIPLES OF ENDOCRINOLOGY

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Summary

This chapter focuses on the basis of the principles of endocrinology. We provide examples of endocrine problems which include functional aspects (under- and over-activity) as well as structural issues related to tumour growth ('endocrine oncology'). We underline the value of the Evidence-Based Medicine as well as the benefits from working within multidisciplinary teams in current clinical endocrinology. This chapter is particularly written in the view of its potential interest for experts in nuclear medicine.

Keywords: endocrinology, principles, endocrine gland, endocrine system, hormone, receptor, feedback loop, Evidence-Based Medicine, endocrine oncology, p53, prognostic marker, predictive marker.

Endocrine glands and system

Endocrine glands are traditionally defined as 'ductless' glandular structures that release their hormonal secretions into the extracellular

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space where they can eventually access circulating plasma and access other tissues. The main difference between the endocrine glands in comparison to other organs is that glands release hormones internally (without using ducts) and do not release substances to the other organs directly or beyond the organism.

The classic endocrine glands include organs such as the pituitary/hypothalamus, thyroid gland, parathyroid glands, pancreatic islets, adrenal glands, ovaries, and testes. Some glands (e.g. the pancreas) not only release hormones but also produces enzymes involved in digestion, and thus have extra-endocrine functions.

The endocrine system consists of three parts: a cell producing hormones, a transport mechanism, and an effector cell (**Figure 1**). The hormones affect only the targeted cells/organs which are able to recognise and are programmed to respond to them. This process happens through activation of receptors.

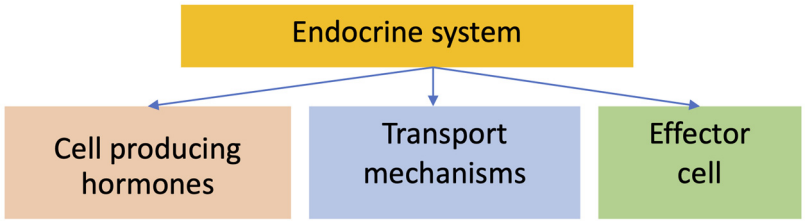


Figure 1. Endocrine system components (cell producing hormones, their transport mechanisms and effector cell).

Hormones

Endocrinology focuses on endocrine glands that produce hormones which are signalling molecules. They carry information between places of secretion and a target tissue through blood and/or extracellular fluids. Hormones regulate physiological functions of the organism including growth, puberty, fertility and metabolism. Some hormones work in opposing pairs e.g. insulin and glucagon.

They can be also secreted from so called “non-traditional endocrine organs” (e.g. the heart - natriuretic peptides; kidney - erythropoietin/renin - adipose tissue – leptin/adiponectin; bone – osteocalcin; and gut - cholecystokinin/incretins) playing critical roles in physiological homeostatic regulation.

The endocrine effects of hormones may lead to activation of processes in a target tissue that is at some distance from the point of their secretion.

To access the target tissue, they travel through the bloodstream, often being bound to plasma proteins. The *paracrine* effect of hormones happens locally, and this process relates to neighbouring cells. If it acts on the secretory cell *itself,* it is known as an *autocrine* effect. Hormones can also act without actually being released from the secretory cell - this process is called an *intracrine* effect (**Figure 2**).

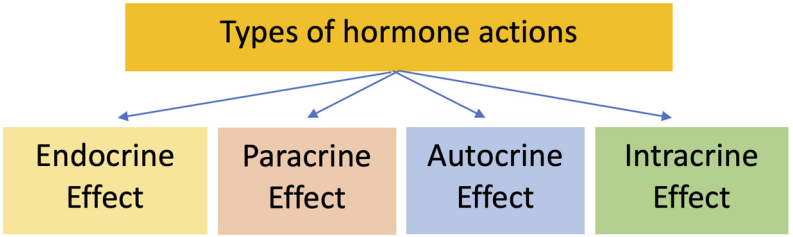


Figure 2. Types of hormone actions. Hormones can act at the site of production: following release (autocrine effect) or without release (intracrine effect) from the producer cell. They can affect neighbouring target cells without entering the circulation (paracrine effect) or through the circulation (endocrine effect).

Hormones may have many and varied chemical compositions. Specific examples include proteins (e.g. adrenocorticotrophin/ACTH), peptides (e.g. vasopressin), monoamines (e.g. norepinephrine/noradrenaline), amino-acid derivatives (e.g. triiodothyronine), steroids (e.g. cortisol), and lipids (e.g. prostaglandins). Proteins can be glycosylated (e.g. thyroid-stimulating hormone) and/or dimerised (e.g. follicle-stimulating hormone) to generate full biological activity.

Receptors

Hormones act in target tissue through receptors to result in their physiological effects. Once in the circulation, hormones bind to these receptors on target tissues to elicit their biological effects. The target tissues for some hormones (e.g. glucocorticoids) can be numerous, reflecting the ubiquitous distribution of their receptors, while those for other tissues have a more limited distribution (e.g. androgens). Endocrine glands do not only produce hormones but may also be a target tissue for their actions.

In target cells/organs, hormones can act through the nucleus (e.g. thyroid hormones, steroids) and/or protein receptors on the cell surface/membrane (e.g. protein, peptide, monoamine, and lipophilic hormones). Some hormones act through both mechanisms (e.g.

triiodothyronine, oestradiol). It may also be possible that the biological "effect" of a hormone reflects a composite of receptor activity located in several different cellular compartments.

Neurotransmitter and peptide hormones interact predominantly with receptors expressed on the plasma membrane on the cell surface. The neurotransmitter-peptide receptor family can be divided into several major groups (**Figure 3a** and **3b**). Examples of ligands for seven-transmembrane domain include e.g. β-adrenergic catecholamines, PTH, LH, FSH, GnRH, TRH, ACTH, MSH, glucagon and dopamine. Single-transmembrane domain ligands include insulin, IGF, EGF and PDGF (growth factor receptors), GH, prolactin, erythropoietin and CSF (cytokine receptors), and natriuretic peptides (guanylyl-cyclase-linked receptors), as well as TGF-β (TGF-β receptor).

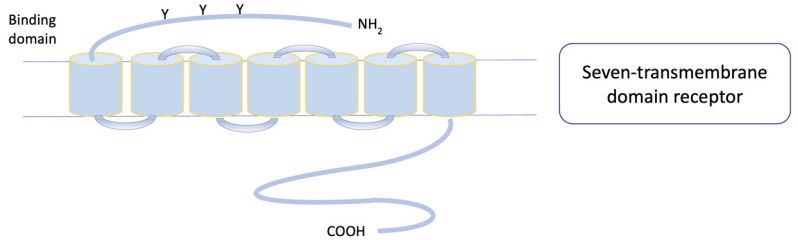
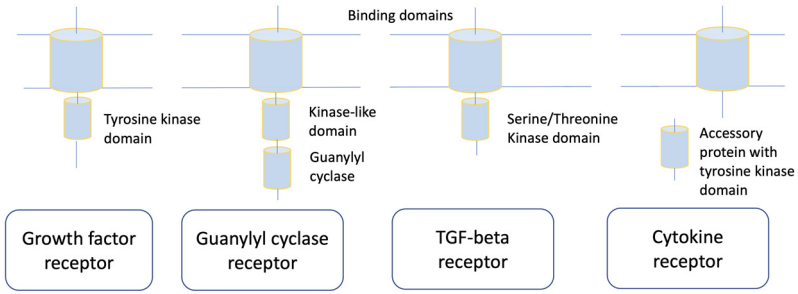


Figure 3a. Seven-transmembrane domain receptor;



3b. Single-transmembrane domain receptor family.

G-protein–coupled receptors (GPCRs) constitute a diverse superfamily of molecules capable of responding to ligands of remarkable structural diversity, ranging from photons to large polypeptide hormones. GPCRs are also the target of over 40% of modern pharmaceuticals.

Somatostatin receptors (SSTRs) belong to the GPCR superfamily. SSTRs first activate a G-protein which then modulates several downstream second messenger systems after binding. Recent evidence indicates that, within the GPCR superfamily, there are mechanisms to increase receptor variability involving generation of splicing variants with less than seven transmembrane domains (TMDs). Such truncated receptors, which may possess their own function or regulate the function of their respective long, canonical receptor isoforms, may be associated with tumour pathology.

The nuclear receptors (NRs) (e.g. for glucocorticoids, mineralocorticoids, androgens, progesterone, oestrogens, thyroid hormone, and vitamin D) differ from the receptors of the surface membrane as they are soluble and generally use transcriptional regulation to promote their biologic effects. Some of them are compartmentalised in the cytoplasm (e.g. the glucocorticoid receptor), whereas others are confined to the nucleus (e.g. the thyroid hormone receptor). They all, however, operate by binding to the nuclear chromatin to initiate the signalling cascade. Based on shared structural and functional properties, NRs consists of two major subtypes: the steroid receptor family (prototypical glucocorticoid receptor, mineralocorticoid receptor, androgen and progesterone receptors) and the thyroid receptor family (thyroid hormone receptor, oestrogen receptor, vitamin D receptor and peroxisome proliferator–activated receptor).

Regulation of hormone level concentration levels

The regulation of hormone levels plays an important role in the control of the biological effects that the hormones exert. Their levels in plasma determine the concentration of the effective ligand at the level of the hormone receptors in peripheral target cells. The main steps include hormone biosynthesis, precursor processing, hormone release, and binding to plasma proteins followed by hormone metabolism (**Figure 4**).

New hormone synthesis raises hormone levels in the circulating plasma. For protein/peptide hormones this usually reflects increased expression of the gene encoding the hormone (through increased production of the mRNA encoding the hormone) with subsequent increases in hormone synthesis. In the case of steroid or thyroid hormones it reflects increased sequestration of precursors for hormone synthesis (cholesterol for steroid hormones or iodide for thyroid hormone) as well as increased activity of enzymatic proteins responsible for executing the individual catalytic events required for hormone production.

Most peptide/protein pre-hormones require a degree of processing to generate the mature hormonal product (for instance, conversion of pro-

insulin to insulin). Alterations in processing activity can impair the ratio of precursor to product in plasma. A critical processing event can be a part of the secretory process itself (e.g. cleavage of thyroxine from thyroglobulin), and impaired processing can result in a dramatic reduction in immunoreactivity as well as bioactivity of the mature hormone.

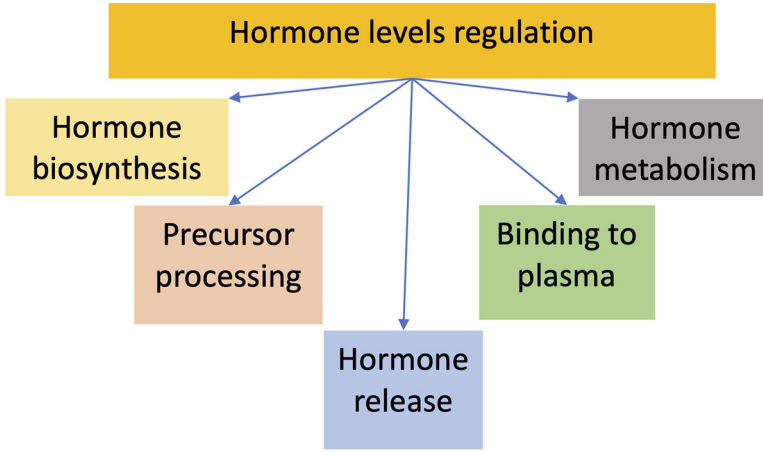


Figure 4. Regulation of hormone levels concentration (hormone biosynthesis, precursor processing, hormone release and binding to plasma, hormone metabolism).

Protein hormones may require post-translational modification (e.g. glycosylation) or assembly (e.g. heterodimerisation) prior to secretion in order to optimise biological activity.

Many hormones (e.g. peptides, proteins, monoamines) are stored in secretory granules in endocrine cells. Release of these granules is promoted by signalling events triggered by exogenous regulators termed secretagogues. This may require activation of a second messenger system in the endocrine cell (e.g. very often cyclic AMP generation or intracellular calcium mobilisation).

Hormone release appears to play the dominant role in controlling steroid hormone levels in circulating plasma, as they are not stored to a significant degree in the hormone-producing cells. Hormones in plasma can circulate either in a free form, un-combined with other molecules, or bound to other molecules such as plasma proteins. The biologically-active fraction of hormone includes free and un-combined forms. However, binding of hormone to plasma proteins provides a reservoir of hormone that exchanges with the free hormone fraction, rendering plasma hormone concentrations

less dependent on hormone synthesis and release, effectively stabilising those concentrations over extended periods of time. This allows for a uniform distribution of hormone concentration in capillary beds perfusing target tissues, and slows hormone metabolism/turnover by sequestering them away from degradative enzymes and/or filtration by the kidney. The more active the degradative mechanisms, the shorter the plasma half-life of the hormone.

Hormone metabolism may be responsible for converting precursors with less hormonal activity to products with greater activity (e.g. conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, or conversion of androstenedione to testosterone). In other cases, metabolism leads to degradation and inactivation of the hormone with a cessation of hormone activity.

Steroids are catalytically converted to inactive metabolites and/or sulfated to promote excretion. Thyroid hormones are subjected to deiodination which blocks their biological activity. Protein and peptide hormones are internalised by target, as well as nontarget, cells, and degraded in intracellular lysosomes.

Feedback loops

Endocrine regulation occurs through feedback loops which may be negative or positive. In a negative feedback loop, the end product/negative regulator can either be an inorganic ion or metabolite (e.g. calcium for PTH) or a hormonal product in the endocrine cascade (e.g. thyroid hormone for TSH). Positive feedback loops (e.g. mid-cycle oestradiol-induced luteinising hormone secretion) also play important roles in physiological homeostasis (**Figure 5**), as well as in pathology.

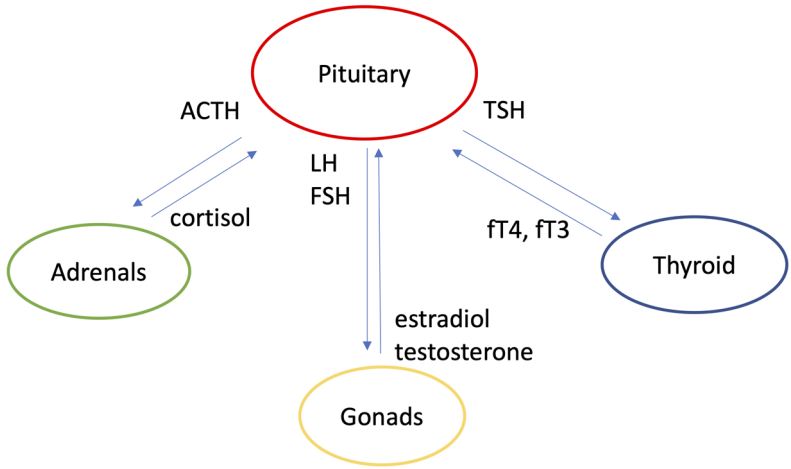


Figure 5. Examples of hormonal feedback loops involving the pituitary gland.

Somatostatin

Somatostatin (SST) is a cyclic peptide and a notable physiological regulator of neuroendocrine function across multiple organ systems. It is produced by the hypothalamus, throughout the central nervous system (CNS), and in different peripheral organs including the gastrointestinal tract (GIT) and pancreas. The SST gene is located on chromosome 3q28 and encodes a 116 amino-acid preprohormone (pre-prosomatostatin) which contains the 92 amino-acid SST prohormone (prosomatostatin). Prosomatostatin is the precursor peptide of the two biologically active SST forms: 14 amino-acid long SST-14 and amino-terminus extended SST-28. The biological roles of the two SST isoforms strongly overlap and the relative proportions of SST-14 to SST-28 change between different tissues. SST-14 is the predominant form in the brain (including the hypothalamus), whereas SST-28 is the major form in the GIT, especially the duodenum and jejunum.

SST has a broad range of biological actions including inhibition of exocrine secretions (gastric acid production, pancreatic enzyme, bile and colonic fluid secretion) and endocrine secretions in the pituitary (GH, TSH, and partially prolactin), pancreas (insulin, gastrin, glucagon) and GIT (cholecystokinin, vasoactive intestinal peptide and secretin). In the CNS, SST is highly expressed in the cortex, lateral septum, extended amygdala, reticular nucleus of the thalamus, hippocampus and many brain stem nuclei, where it acts as a neurotransmitter and neuromodulator.

There are five SSTR subtypes, each encoded by five separate genes on five separate chromosomes: 14, 17, 22, 20 and 16, respectively. Sequence homology is 39–57% among the five subtypes. SSTRs belong to the G-protein coupled receptor (GPCR) superfamily and are extensively distributed throughout many tissues ranging from the CNS to the pancreas and gut, and also in pituitary, kidney, thyroid, lung and immune cells, besides their presence in various cancer cells. The majority of tumours (and also normal tissues) express SSTR2, followed by SSTR1, SSTR5 and SSTR3, whereas SSTR4 is the least expressed subtype. There are two different isoforms of SSTR2 (SSTR2A and SSTR2B) produced via alternative splicing, and SSTR2B is very poorly expressed in the human. SSTRs bind natural peptides, SST-14 and SST-28, with similar high affinity (nM range). However, SSTR5 has a 10-fold higher affinity for SST-28 compared to SSTR2A or SSTR3, which have a higher affinity to SST-14.

The somatostatin receptor (SSTR) as a GPCR

SSTRs belong to the GPCR superfamily. Binding of SST to its corresponding GPCR (SSTRs) triggers a cyclical activation and inactivation process in the G protein whereas the signal is transduced intracellularly. GPCRs are components of multiprotein networks, called ‘receptosomes’, which are organised around scaffolding proteins. GPCR-interacting proteins (GIPs), regulators of G-protein signalling (RGS) and GPCR kinases (GRKs) are the main proteins that are known to effect GPCR signalling after ligand binding. GIPs are transmembrane or cytosolic proteins which may alter either binding or functional responses of the GPCR resulting in an abundance of potential receptor–protein connections. GRKs play key roles in the fundamental pathways leading to phosphorylation-dependent GPCR desensitisation, endocytosis, intracellular trafficking and re-sensitisation, as well as in the modulation of important intracellular signalling cascades by GPCR.

Anti-tumour effects of somatostatin

There are a number of mechanisms responsible for the anti-tumour actions of SST. These are the direct blockade of cell cycle progression through the activation of phosphotyrosine phosphatases (PTPs), the indirect influence on tumour growth mediated by the inhibition of the production of growth factors that sustain tumour development, and an anti-

angiogenic effect that involves the regulation of the activity of both endothelial cells and monocytes[1,2].

In general, SSTR1, SSTR2, SSTR4 and SSTR5 produce cytostatic effects through similar downstream effector pathways, whereas SSTR2 and SSTR3 induces pro-apoptotic (cytotoxic) signals when activated. SST suppresses insulin-like growth factor (IGF)-I serum levels through a direct inhibition of its gene expression or through the inhibition of GH secretion from the pituitary and the consequent reduction of GH-stimulated IGF-1 production in the liver. SST analogues inhibit the secretion of autocrine/paracrine effectors of tumour cell survival such as the IGF-1 and -2, EGF, interleukin-6 and the transforming growth factor family. The attenuation of secretion of such survival factors in the tumour microenvironment accordingly establishes an autocrine/paracrine anti-proliferative effect. For the anti-angiogenic activity of SSTRs, three signal pathways have been identified: inhibition of endothelial cell activity (proliferation, migration and invasion), inhibition of the synthesis and secretion of pro-angiogenic factors such as vascular endothelial growth factor and basic fibroblast growth factor, and inhibition of monocyte activation. Native SST inhibits the secretion and proliferation of both normal and neoplastic pituitary cells by inducing several intracellular pathways, depending on receptor subtype and target tissue.

In summary, SST is a peptide hormone which acts mainly as an inhibitor in many endocrine systems. SST has five receptor sub- types (SSTR1–5) with SSTR2 as the most commonly expressed form in both normal and tumoral tissues. SST has been widely investigated for its anti-tumoral effects and their mechanisms, and currently there are three SST analogues (lanreotide, octreotide, pasireotide) in clinical use. The anti-proliferative action of SST mainly occurs through phosphotyrosine phosphatases which modulate MAPK and PI3K/Akt pathways, whereas its anti-secretory action occurs through decreased intracellular cAMP, K^+ and Ca^{++} levels.

Principles of clinical endocrinology

Clinical endocrinology relates to disorders of the endocrine glands. The problems may result from alteration in hormone production or may be related to the gland as a structural organ itself. Based on the view that this chapter is dedicated to experts in nuclear medicine, we have prepared a succinct summary regarding the most important aspects of the endocrine glands to aid in understanding clinical principles. This chapter will include a summary of thyroid problems as an example of under- and overactivity

of the gland, while pituitary tumours will be used to illustrate endocrine oncology.

Disorders of the endocrine gland can relate to their function and/or structure. As these glands produce hormones, functional alterations may result in hormone under- or over-production (e.g. under- and over-active thyroid, parathyroid glands or pituitary and adrenals). The main pathological processes affecting hormonal glands include auto-immunity, infective and non-infective inflammation, tumorigenesis in the glands, or metastases of other cancers to the endocrine glands. The function of the endocrine gland can also be affected by surgical removal – total or partial, as for thyroid disease. Some glands' hormonal production changes over the lifetime e.g. the ovaries, where physiologically hormonal production decreases in the menopause, in which case the interpretation of hormone levels will depend on the patient's age.

Thyroid

Anatomically, the thyroid consists of two lateral lobes extending upward over the lower half of the thyroid cartilage, being connected by an isthmus that lays horizontally just below the cricoid cartilage. Biosynthesis of thyroid hormones requires iodine as a substrate., for which there are specific uptake mechanisms. The thyroid is the only source of T4 and secretes 20% of circulating T3. The rest of the T3 remains generated in the extra-glandular tissues by conversion of T4 to T3 by deiodinases (mostly in liver and kidneys). The metabolic state correlates more closely with the free than the total hormone concentration in the plasma. The levels of thyroid hormones in the blood are tightly controlled by feedback mechanisms involved in the hypothalamo-pituitary-thyroid (HPT) axis, with thyroid stimulating hormone (TSH) being produced by the pituitary (**Table 1**). TSH is in turn principally regulated by hypothalamic TRH, and the overall negative feedback loop appears to be tightly set at or shortly after birth, thereafter remaining constant. Radiologically, the most useful and common imaging in modern thyroidology includes thyroid US, scinti-scanning (nuclear medicine scans), CT and PET.

Table 1. Thyroid hormone concentrations in various thyroid disorders

Condition	TSH	fT4	fT3
Primary hyperthyroidism	undetectable	⇑⇑	⇑
T3 toxicosis	undetectable	normal	⇑⇑
Subclinical hyperthyroidism	⇓	normal	normal
Secondary hyperthyroidism (TSH-oma)	⇑ or normal	⇑	⇑
Thyroid hormone resistance	⇑ or normal	⇑	⇑
Primary hypothyroidism	⇑	⇓	⇓ or normal
Subclinical hypothyroidism	⇑	normal	normal
Secondary hypothyroidism	⇓ or normal	⇓	⇓ or normal

Table 2. Aetiologies of thyrotoxicosis

Excessive thyroid stimulation	Graves' disease Hashitoxicosis Pituitary TSH-oma Pituitary thyroid hormone resistance syndrome Trophoblastic tumours producing hCG with thyrotrophic activity
Thyroid nodule with autonomous hormones production	Toxic solitary nodule Toxic multinodular goitre Thyroid cancer (very rarely)
Thyroid inflammation	Silent thyroiditis Post-partum thyroiditis Subacute (de Quervain's) thyroiditis Drug induced thyroiditis (amiodarone)

Exogenous thyroid hormones	Overtreatment with thyroid hormones Thyrotoxicosis factitia
Ectopic thyroid tissue	Metastatic thyroid cancer Struma ovarii

The principal thyroid problems include over- and underactivity, thyroiditis and tumours of the thyroid. The most common causes of **thyrotoxicosis** or hyperthyroidism are outlined in **Table 2**. Symptomatically, hyperthyroidism presents with hyperactivity, irritability, altered mood, insomnia, heat intolerance, sweating, palpations, fatigue, weakness, weight loss, and increased stool frequency. The main treatment modalities include medical anti-thyroid therapy, radioiodine (RAI) and surgery. **Nodular thyroid disease** relates tothe presence of a single or multiple palpable or non-palpable nodules within the thyroid gland, with prevalence rates ranging between 5% and 50%. Nodules are more likely to be malignant in patients <20 and >60 years of age. Investigation useful in the work up for the thyroid nodules include fine needle aspiration cytology (FNAC), thyroid hormone profiles, respiratory flow loops as well as CT/MRI scans. Treatment of toxic thyroid goitre include anti-thyroid medications, RAI and surgery. The main causes of **thyroiditis** and **hypothyroidism** are summarised in **Tables 3** and **4**, respectively. High titres of anti-thyroid peroxidase (anti-TPO) antibodies, anti-thyroglobulin and/or TSH-receptor antibodies are commonly found in patients with autoimmune thyroid disease (Hashimoto's thyroiditis, Graves' disease), but can also be found in euthyroid individuals.

Table 3. Causes and characteristics of thyroiditis

Cause	Characteristic features
Autoimmune	Grossly lymphocytic and fibrotic hypo- or hyperthyroidism
Post-partum	Lymphocytic, transient thyrotoxicosis or hypothyroidism
Drug-induced	Amiodarone, interferon alfa
Subacute (de Quervain's)	Multinuclear giant cells
Riedel's	Extensive fibrosis of thyroid

Radiation	Radiation injury, transient thyrotoxicosis
Pyogenic (rare)	Stephylococcus aureus, Streptococci, E. coli, tuberculosis, fungal

Table 4. Classification of the causes of hypothyroidism

Non-goitrous	Post-ablation (radioiodine, surgery)
	Congenital development defect
	Atrophic thyroiditis
	Post-irradiation (e.g. for lymphoma)
Goitrous	Chronic Hashimoto's thyroiditis
	Transient de Quervain's thyroiditis
	Iodine deficiency
	Drug-elicited (amiodarone, iodides, lithium, amino salicylic acid, aminoglutethimide, interferon alfa thalidomide, sunitinib, rifampicine)
	Haemochromatosis
	Heritable biosynthesis defects
	Maternally transmitted (e.g antithyroid agents, iodides)
Pituitary	Panhypopituitarism
	Isolated TSH deficiency
	Drugs (bexarotene)
Hypothalamic	Neoplasm
	Infiltrative (sarcoidosis)
	Congenital defect
	Infection (encephalitis)

Endocrine oncology

Endocrine oncology focuses on tumours of the hormone producing glands including the thyroid, parathyroid, pituitary, pancreas and adrenals. The term neuroendocrine tumour (NET) refers to a heterogeneous group of malignancies. The term "neuroendocrine" is applied to widely dispersed cells with "neuro" and "endocrine" properties[3]. The "neuro" property is based on the identification of dense-core granules that are similar to granules present in serotoninergic neurons, which store monoamines (unlike neurons, however, NE cells do not contain synapses). The "endocrine" property refers to the synthesis and secretion of these

monoamines. The neuroendocrine (NE) system includes endocrine glands, such as the pituitary, the parathyroids, and the NE adrenal, as well as endocrine islet tissue embedded within glandular tissue (thyroid or pancreatic) and scattered cells in the exocrine parenchyma, such as endocrine cells of the digestive and respiratory tracts, which belong to what is known as the *diffuse endocrine system*.

Recent consensus guidelines published by Asa and colleagues in 2017[4], based in part on the new 2017 World Health Organization (WHO) classification[5,6], suggest that we should abandon the term 'pituitary adenoma' entirely in terms of these all being pituitary neuroendocrine tumours (PitNETs), with a variable propensity for invasion and malignancy, as for other NETs. However, this recommendation is controversial and not accepted by all endocrinologists. In this chapter we will use the term pituitary tumours as an example of the complexity of endocrine oncology.

Pituitary tumours are unique in multiple ways[7]. They comprise approximately 10–15% of intracranial tumours. They may be functioning or non-functioning and therefore present with a huge variety of symptoms (**Table 5**). Most of pituitary tumours are non-invasive, showing slow growth and remaining within the pituitary fossa and/or displacing the surrounding tissues; however, up to 25–55% of pituitary adenomas (PAs) may show characteristics that are invasive and infiltrate surrounding structures, including the cavernous sinuses, bone, sphenoid sinuses, and, less commonly, nerve sheaths. However, truly 'aggressive' tumors are less common[8,9]. Pituitary carcinomas (PCs) are a rare clinical entity that represent only 0.1–0.2% of all pituitary tumours but result in a high mortality rate[10].

Table 5. Functioning pituitary tumours and their selective clinical symptoms

Prolactinoma	Galactorrhoea Disturbed gonadal functions Headaches
Growth hormone producing (Acromegaly)	Increased sweating Headaches Change in the ring/shoe sizes Changes in facia appearance Tongue enlargement Hypertension Insulin resistance

	OSA Colonic polyps
ACTH producing (Cushing's disease)	Weight gain Facial appearance Thin skin Easy bruising Red striae Proximal muscle weakness Mood swings Menstrual disturbances Hypertension Diabetes Decreased bone density mass
TSH producing	Typical for hyperthyroidism
Gonadotrophin-secreting	Premenopausal women: Menstrual irregularities (oligo-/amenorrhoea, spotting-menorrhagia), infertility, galactorrhoea mass effects (headaches, visual deterioration) ovarian hyperstimulation syndrome. Men: Testicular enlargement hypogonadism, mass effects (headaches, visual deterioration)

While PAs are rarely malignant, they may be aggressive. Aggressive behaviour of the PA is characterised as a particularly invasive (radiologically and/or intraoperatively), unusually rapid tumour growth rate and/or recurrent behaviour, and/or clinically relevant tumour growth despite optimal standard therapies (surgery, radiotherapy and conventional medical treatments)[8,9].

Based on the 2004 WHO classification, pituitary tumours were previously divided into typical, atypical and carcinomas. Current WHO criteria have abandoned grading tumours as 'atypical' due to its limited prognostic value**.** It is now recommended (WHO 2017) to principally classify PAs in terms of their radiological invasive characteristics as well as their histopathological proliferation index, Ki-67.

Oncological malignant potential of pituitary tumours is defined by the ability to metastasise (including craniospinal and/or systemic metastases). Early identification of pituitary carcinoma is difficult yet remains crucial to appropriate management. As noted above, establishing predictive and/or prognostic markers of clinical aggressiveness remains problematic and is a 'work in progress'.

Endocrine evaluation is required in all such cases of patients with aggressive tumours, and either site-specific symptoms or discordant biochemical and radiological findings, while ocacsionally screening for metastatic disease to diagnose PC is required.

The diagnosis of a pituitary carcinoma is often preceded by the presence of unusual symptoms such as hearing loss, ataxia, motor impairment or a neck mass, prompting further diagnostic testing. Metastases rarely dominate the clinical picture in the early stages of disease and, at times, cases are only discovered post-mortem. Early identification of pituitary tumours at risk for progression to pituitary carcinoma is difficult, and no combination of histopathological or immunohistochemical analyses has conclusively been able to identify PAs that will progress to carcinoma. Suspicion should be raised when patients present with tumours of aggressive subtypes and histological features and with multiple recurrences.

Molecular biology of pituitary tumours

The pathogenesis of tumour formation in the anterior pituitary has been intensively studied, but the causative mechanisms involved in pituitary cell transformation and tumourigenesis remain elusive[7]. Most pituitary tumours are sporadic, but some arise as a component of genetic syndromes such as the McCune–Albright syndrome, multiple endocrine neoplasia type 1, Carney complex and, the most recently described, a MEN1-like phenotype (MEN4) and some pituitary adenoma predisposition syndromes (familial isolated pituitary adenoma, FIPA). Some specific genes have been identified that predispose to pituitary neoplasia (*GNAS, MEN1, PRKAR1A, CDKN1B* and *AIP*), but these are rarely involved in the pathogenesis of sporadic tumours. Mutations of tumour suppressor genes or oncogenes, as seen in more common cancers, do not seem to play an important role in the great majority of pituitary adenomas. The pituitary tumour transforming gene (PTTG; securin) was the first transforming gene found to be highly expressed in pituitary tumour cells, and seems to play an important role in the process of oncogenesis. Many tumour suppressor genes, especially those involved in the regulation of the cell cycle, are

under-expressed, most often by epigenetic modulation – usually promoter hypermethylation – but the regulator of these co-ordinated series of methylations is also unclear. Cell signalling abnormalities have been identified in pituitary tumours, but their genetic basis is unknown. Both Raf/MEK/ERK and PI3K/Akt/mTOR pathways are over-expressed and/or over-activated in pituitary tumours: these pathways share a common root, including initial activation related to the tyrosine kinase receptor, and some researchers speculate that a change to these receptors or their relationship to membrane matrix-related proteins may be an early event in pituitary tumourigenesis. In some secretory tumour phenotypes, some driver somatic mutations have been identified, including Gsα in some 20% of somatotrophinomas and USP8 in up to 40% of corticotroph tumours.

Pituitary carcinomas rarely occur in genetic syndromes; however examples of PC patients with MEN1, mutations have been documented, while *AIP, PRKAR1A, DICER1* and *GPR101* mutations have not been associated with metastatic spread to date, although there is one report of a PC in a patients with an *SDH-B* germline mutation. There is evidence that factors involved in cell cycle progression, angiogenesis, metastases, invasion and upregulation of cyclin D1, VEGF, MMP-9, miRNAs and p21Cip1, may all contribute to malignant transformation of adenomas to PCs. Down-regulated factors including MGMT, p16Ink4A, p27Kip1, Bcl-2, Bax, Bcl-x and MT3 seam to be involved in the cell cycle, apoptosis, tumour suppression and metabolism. Highly aggressive pituitary tumours or PCs may show a response to the chemotherapeutic agent temozolomide.

Endocrine oncology vs classical oncology

There are several differences in the way we view pituitary tumours, especially malignant and aggressive ones. These discrepancies do not only differentiate such tumours from ‘classical’ oncology but are also quite heterogeneous in endocrine oncology itself. However, over the last few years, the pituitary community has changed its approach. PAs are no longer considered as a specific endocrine disease but rather as true tumours and cannot be readily divided into simply ‘adenomas’ vs ‘carcinomas’. Similar to other NETs, all may be considered to have ‘malignant’ potential, malignancy being defined as local invasiveness and recurrence, and resistance to therapy, with PCs just one end of the spectrum of PitNETs[4]. This more oncological approach permits the appropriate use of chemotherapeutic drugs in some conditions and a better stratification and personalisation of the therapeutic options offered to patients. This new classificatory approach is similar to that applied to NETs.

The classical understanding of the predictive factors relates to their value of prediction in response to particular treatments, whereas prognostic factors influence patient survival (overall-, disease-free or progression-free survival). These terms are used in endocrine oncology in a 'liberal' and promiscuous manner, which renders analysis difficult when comparing different sets of results.

p53 tumour suppressor protein

p53 protein is a product of the tumour suppressor gene playing a role in apoptosis, inhibition of angiogenesis and genomic stability. The prognostic value of its expression has been previously assessed in many cancers. Physiologic levels of p53 typically are not detectable by immunohistochemistry due to the short half-life of wild-type p53: some mutations of the P53 gene may result in p53 protein nuclear accumulation (due to extension of its half-life), allowing for its immunohistochemical detection. The reliability of p53 as a marker of clinical invasiveness in pituitary tumours is still a subject of debate. For this reason, the new 2017 WHO classification advises that it is not a useful marker for aggressiveness for routine use, although in some circumstances it may aid in decision making.

Tumour proliferation

The MIB-1 labelling index (LI) stains for the Ki-67 antigen and is associated with cell proliferation. Recent work has demonstrated that it acts as a surfactant to separate chromosomes during mitosis and is thus a marker of cell division. It is upregulated in dividing cells and involved in ribosomal RNA transcription. Since the initial description of Ki-67 in PAs by Burger et al. in 1986, multiple researchers have attempted to correlate its value with clinicopathological parameters and its predictive and prognostic value, much as has been achieved with NETs. To help inform potential predictors of tumours aggressiveness in pituitary tumours, the *European Society of Endocrinology* (ESE) guidelines recommend histopathological analysis, which should include as a minimum immunodetection of pituitary hormones and Ki-67 proliferation index evaluation[8,9]. They also recommend p53 immunodetection and the evaluation of the mitotic count when the Ki-67 index is ≥3%. The ESE recommendations also suggest that interpretation of histopathological results should be in the clinical, radiological and surgical context of the

individual patient, with the particular caveat that no marker alone is sufficient to predict tumour behaviour.

Histology

The WHO classification of tumours of endocrine organs was revised in 2017 (4th edition). This new classification has been reviewed in several updated and very comprehensive papers. According to recent knowledge on tumour development and prognosis, important changes in the new classification of PAs were introduced. The new classification focuses on adeno-hypophyseal-cell lineage for the designation of a pituitary adenoma. Based on this classification, assessment of pituitary transcription factors is also recommended to complement an accurate diagnosis, especially in hormone-negative tumours[11]. Subsequently, based on this revision, 'null cell adenomas' have been shown to be extremely rare, as ultrasensitive techniques have shown that the majority of previously reported 'null cell' adenomas are in fact gonadotroph in origin.

There are three major pathways of adeno-hypophyseal cell differentiation and relevant transcription factors: corticotrophs (demonstrable by the T-box pituitary transcription factor (T-pit)), somatotrophs/lactotrophs/mammo-somatotrophs/thyrotrophs (demonstrable by pituitary transcription factor 1 (Pit-1)), and gonadotrophs (demonstrable by steroidogenic factor-1 (SF-1) and/or GATA-2 in the presence of oestrogen receptor-α, ERα). (**Figure 6**).

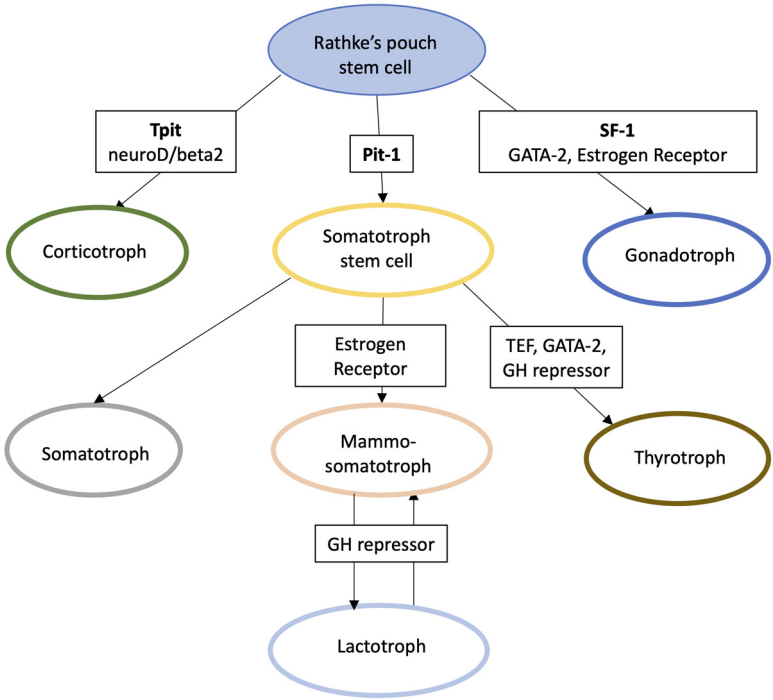


Figure 6. Adenohypophysial cell lineage and the transcription factors (Figure adapted from Nishioka et al. 2018. Corticotroph are determined by T-pit and neuro D1; gonadotrophs are determined SF-1, GATA-2 and ER; Somato-, Lacto- and Thyrotroph are determined by Pit-1).

Progression and malignant transformation

The malignant transformation of a 'benign' pituitary adenoma has always been a matter of controversy, and the progression from benign to aggressive/malignant character poorly understood. PCs are thought to arise either *de novo*, or more frequently, from a malignant transformation of a pre-existing 'benign' adenoma. Highly aggressive transformation, including that to a carcinoma, is rare, and mainly occurs in prolactin- and ACTH-secreting tumours, possibly because these tumours are less likely to show markers of senescence, compared with those of other adenoma types. It is unclear what proportion of these aggressive adenomas will progress into carcinomas, and most importantly, how to predict when this is likely. When non-compliance is ruled out, escape from the control by initial