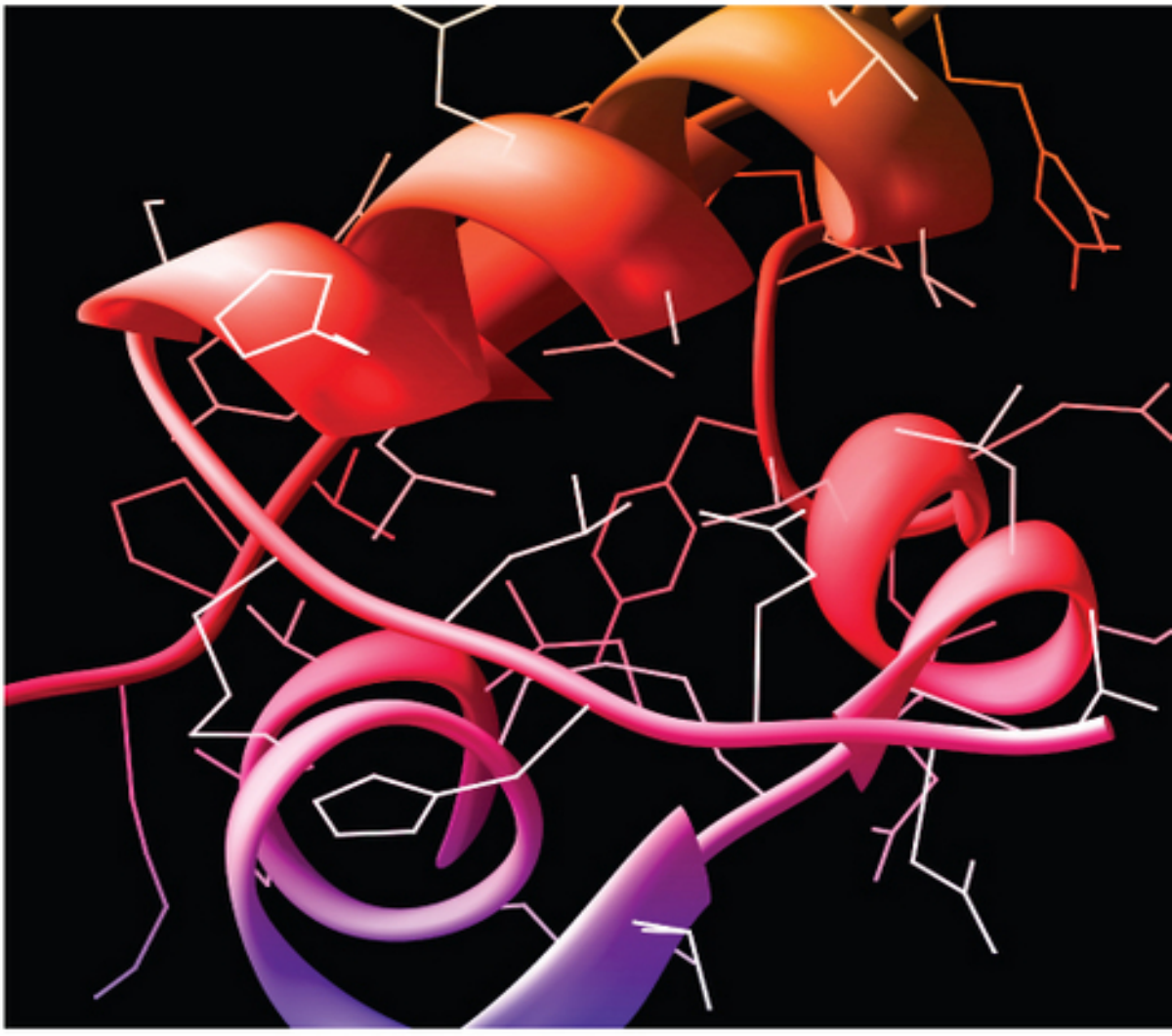
LECTURE NOTES

Endocrinology and Diabetes

AMIR SAM
KARIM MEERAN



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Lecture Notes

Endocrinology and Diabetes

Amir Sam

BSc (Hons), MB BS (Hons), MRCP
Wellcome Trust Clinical Research Fellow and SpR in Endocrinology and Diabetes, Hammersmith Hospital, Imperial College, London, UK

Karim Meeran

MD, FRCP, FRCPath
Professor of Endocrinology, Imperial College Healthcare NHS Trust, London, UK

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Preface

In the conception of this book, we used our teaching experience to cover the main topics in endocrinology and diabetes in a simple and easy-to-understand style.

We have tried to discuss the basic anatomy and physiology of the endocrine system, which is fundamental to the understanding of pathophysiology and presentation of the endocrine diseases. *Lecture Notes: Endocrinology and Diabetes* also contains detailed sections on the practical management of diabetes and endocrine disorders. Therefore we believe that this book is suitable for medical students and doctors training in endocrinology, and can be used for exam revision as well as rapid consultation in the clinic.

Amir Sam
Karim Meeran

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Abbreviations

5-HIAA 5-hydroxyindoleacetic acid
ABPI ankle–brachial pressure index
ACCORD Action to Control Cardiovascular Risk in Diabetes trial
ACE angiotensin-converting enzyme
ACR albumin-to-creatinine ratio
ACTH adrenocorticotrophic hormone
ADH antidiuretic hormone
ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial
AGB adjustable gastric banding
AGE advanced glycosylation end-product
AHO Albright's hereditary osteodystrophy
AIDS acquired immune deficiency syndrome
ALT alanine transaminase
AMPK adenosine monophosphate-activated protein kinase
APS autoimmune polyglandular syndrome
ARB angiotensin receptor blocker
AVP arginine vasopressin
BFGF basic fibroblast growth factor
BMD bone mineral density
BMI body mass index
BMP-7 bone morphogenic protein-7
CAH congenital adrenal hyperplasia
CARDS Collaborative AtoRvastatin Diabetes Study
CARE Cholesterol and Recurrent Events trial
CDGP constitutional delay of growth and puberty

CEA carcinoembryonic antigen
CNS central nervous system
CPT I carnitine palmitoyltransferase-I
CRH corticotrophin-releasing hormone
CSW cerebral salt wasting
CT computed tomography
CTLA-4 cytotoxic T-lymphocyte antigen 4
CVD cardiovascular disease
DAFNE Dose Adjustment for Normal Eating
DCCT Diabetes Control and Complications Trial
DEXA dual-energy X-ray absorptiometry
DHEA dehydroepiandrosterone
DHEA-S dehydroepiandrosterone sulphate
DIEP Diabetes in Early Pregnancy study
DKA diabetic ketoacidosis
DMSA dimercaptosuccinic acid
DPP-IV dipeptidyl peptidase-IV
ECG electrocardiogram
EDIC Epidemiology of Diabetes Interventions and Complications study
eGFR estimated glomerular filtration rate
ESR erythrocyte sedimentation rate
ESRD end-stage renal disease
FIELD Fenofibrate Intervention and Event Lowering in Diabetes study
FNA fine needle aspiration
FSH follicle-stimulating hormone
GAD glutamic acid decarboxylase
GEMINI Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives
GFR glomerular filtration rate
GH growth hormone
GHRH growth hormone-releasing hormone

GLP-1 glucagon-like peptide-1
GSH glucocorticoid-suppressible hyperaldosteronism
HbA_{1c} glycated haemoglobin
hCG human chorionic gonadotrophin
HDL high-density lipoprotein
HHS hyperosmolar hyperglycaemic state
HIF hypoxia-inducible factor
HIV human immunodeficiency virus
HPA hypothalamic–pituitary–adrenal
HRT hormone replacement therapy
ICSI intracytoplasmic sperm injection
IGF-I insulin-like growth factor-I
IGFBP-3 insulin-like growth factor-binding protein-3
IRMA intraretinal microvascular abnormality
IRS insulin receptor substrate
ITT insulin tolerance test
IVF in vitro fertilization
JNK c-Jun amino-terminal kinase
LADA latent autoimmune diabetes in adults
LDL low-density lipoprotein
LH luteinizing hormone
MAPK mitogen-activated protein kinase
MC4R melanocortin-4 receptor
MDRD Modification of Diet in Renal Disease study
MEN multiple endocrine neoplasia
MI myocardial infarction
MODY maturity-onset diabetes of the young
MRI magnetic resonance imaging
MSH melanocyte-stimulating hormone
MTC medullary thyroid carcinoma
NET neuroendocrine tumour
NF neurofibromatosis
NPH neutral protamine Hagedorn

NSAID non-steroidal anti-inflammatory drug
NSC National Screening Committee
NVD new vessels on disc
NVE new vessels elsewhere
OGTT oral glucose tolerance test
PAC plasma aldosterone concentration
PCOS polycystic ovary syndrome
POMC proopiomelanocortin
POPADAD Prevention of Progression of Arterial Disease and Diabetes study
PPAR peroxisome proliferator-activated receptor
PPNAD primary pigmented nodular adrenocortical disease
PRA plasma renin activity
PSA prostate-specific antigen
PTH parathyroid hormone
PTTG pituitary tumour transforming gene
PTU propylthiouracil
PYY peptide YY
RANK receptor activator of nuclear factor kappa B
RANKL RANK ligand
RYGB roux-en-Y gastric bypass
SD standard deviation
SDHB succinate dehydrogenase subunit B
SG specific gravity
SHBG sex hormone-binding globulin
SIADH syndrome of inappropriate antidiuretic hormone
SOS Swedish Obese Subjects study
SRS somatostatin receptor scintigraphy
StAR steroidogenic acute regulatory protein
STAT signal transduction and activators of transcription
T_3 triiodothyronine
T_4 thyroxine

TGF transforming growth factor
TNF tumour necrosis factor
TRAb thyroid-stimulating hormone receptor antibody
TRH thyrotrophin-releasing hormone
TSH thyroid-stimulating hormone
UKPDS United Kingdom Prospective Diabetes Study
VEGF vascular endothelial growth factor
WHI Women’s Health Initiative trials
WHO World Health Organization

Chapter 1

Thyroid anatomy and physiology

Anatomy

The thyroid gland consists of left and right *lobes* connected by a midline isthmus (Fig. 1.1). The isthmus lies below the cricoid cartilage, and the lobes extend upward over the lower half of the thyroid cartilage. The thyroid is covered by the strap muscles of the neck and overlapped by the sternocleidomastoids. The pretracheal fascia encloses the thyroid gland and attaches it to the larynx and the trachea. This accounts for the upward movement of the thyroid gland on swallowing.

The thyroid gland develops from the floor of the pharynx in the position of the foramen caecum of the adult tongue as a downgrowth that descends into the neck. During this descent, the thyroid gland remains connected to the tongue by the thyroglossal duct, which later disappears. However, aberrant thyroid tissue or thyroglossal cysts (cystic remnants of the thyroglossal duct) may occur anywhere along the course of the duct (Fig. 1.2). Such thyroid remnants move upward when the tongue is protruded.

The thyroid gland is composed of epithelial spheres called *follicles* (Fig 1.3), whose lumens are filled with a proteinaceous colloid containing *thyroglobulin*. Two basic cell types are present in the follicles. The follicular cells secrete thyroxine (T_4) and triiodothyronine (T_3) and

originate from a downward growth of the endoderm of the floor of the pharynx (see above). The parafollicular or C cells secrete calcitonin and arise from neural crest cells that migrate into the developing thyroid gland. The follicles are surrounded by an extensive capillary network.

Physiology

Thyroid hormones act on many tissues. They regulate:

- organogenesis, growth and development (central nervous system, bone)
- energy expenditure
- protein, carbohydrate and fat metabolism
- gut motility
- bone turnover
- heart rate and contractility, and peripheral vascular resistance
- beta-adrenergic receptor expression
- muscle contraction and relaxation
- the menstrual cycle
- erythropoiesis.

Iodine is essential for normal thyroid function. It is obtained by the ingestion of foods such as seafood, seaweed, kelp, dairy products, some vegetables and iodized salt. The recommended iodine intake for adults is 150 µg per day (250 µg per day for pregnant and lactating women). Dietary iodine is absorbed as iodide. Iodide is excreted in the urine.

Figure 1.1 Thyroid gland.

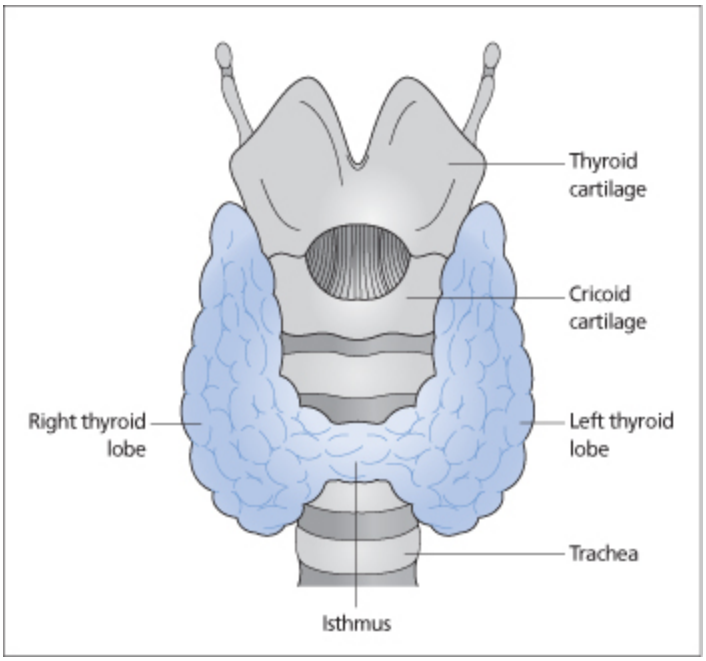
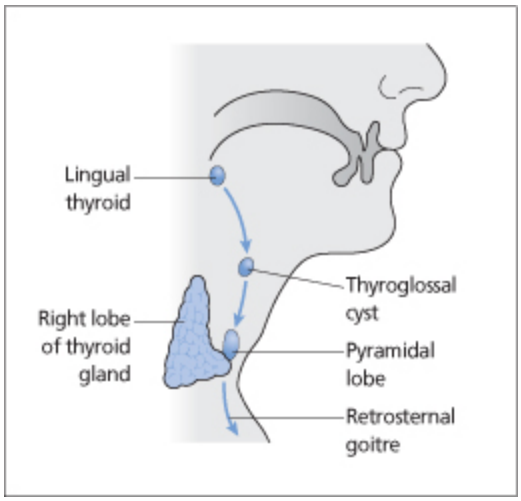


Figure 1.2 Possible sites of remnants of the thyroglossal duct.



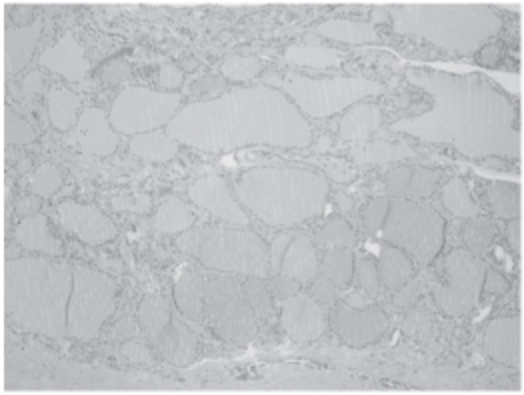
Thyroid hormone synthesis

Figure 1.4 illustrates different steps in thyroid hormone synthesis:

- *Thyroglobulin* is synthesized in the rough endoplasmic reticulum and is transported into the follicular lumen by exocytosis.

- Iodide is transported into the thyroid follicular cells via a sodium–iodide symporter on the basolateral membrane of the follicular cells. Iodide transport requires oxidative metabolism.
- Inside the follicular cells, iodide diffuses to the apical surface and is transported by pendrin (a membrane iodide–chloride transporter) into the follicular lumen.
- *Thyroid peroxidase* (TPO) enzyme catalyzes the process of oxidation of the iodide to iodine and its binding (organification) to the tyrosine residues of thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).
- DIT and MIT molecules are linked by TPO to form *thyroxine* (T_4) and *triiodothyronine* (T_3) in a process known as coupling.
- Thyroglobulin containing T_4 and T_3 is resorbed into the follicular cells by endocytosis and is cleaved by lysosomal enzymes (proteases and peptidases) to release T_4 and T_3. T_4 and T_3 are then secreted into the circulation.
- Uncoupled MIT and DIT are deiodinated, and the free tyrosine and iodide are recycled.

Figure 1.3 (a) A low-power histological image of thyroid tissue showing numerous follicles filled with colloid and lined by cuboidal epithelium. (b) A high-power view of follicles lined by cuboidal epithelium. (c) Thyroid follicles (lined by follicular cells), surrounding capillaries and parafollicular cells.



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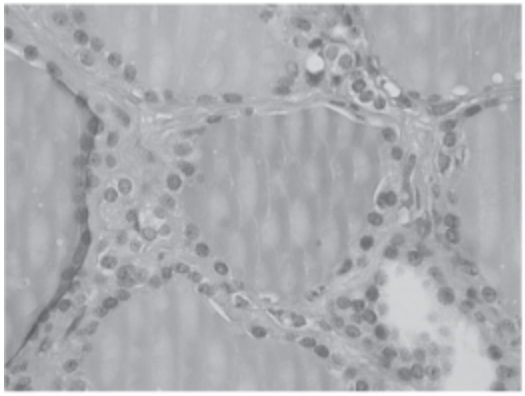

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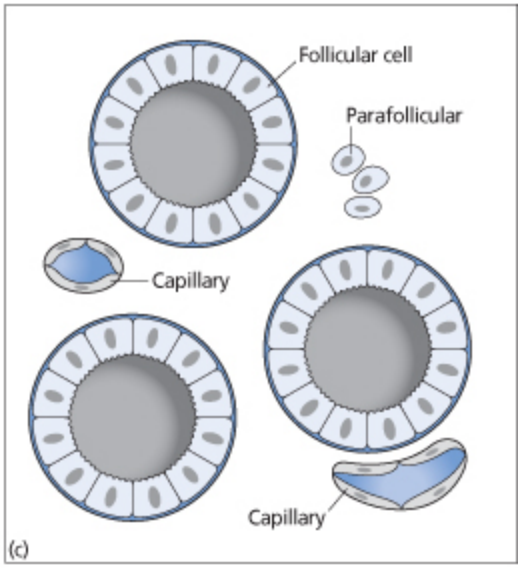


The thyroid gland stores T_4 and T_3 incorporated in thyroglobulin, and can therefore secrete T_4 and T_3 more quickly than if they had to be synthesized.

Extra-thyroidal T_3 production

T_4 is produced entirely by the thyroid gland. The production rate of T_4 is about 100 µg per day. However, only 20% of T_3 is produced directly by the thyroid gland (by coupling of MIT and DIT). Around 80% of T_3 is produced by the deiodination of T_4 in peripheral extra-thyroidal tissues (mainly liver and kidney). The total daily production rate of T_3 is about 35µg.

T_4 is converted to T_3 (the biologically active metabolite) by *5′-deiodination* (outer-ring deiodination). 5′-Deiodination is mediated by deiodinases type 1 (D1) and type 2 (D2). D1

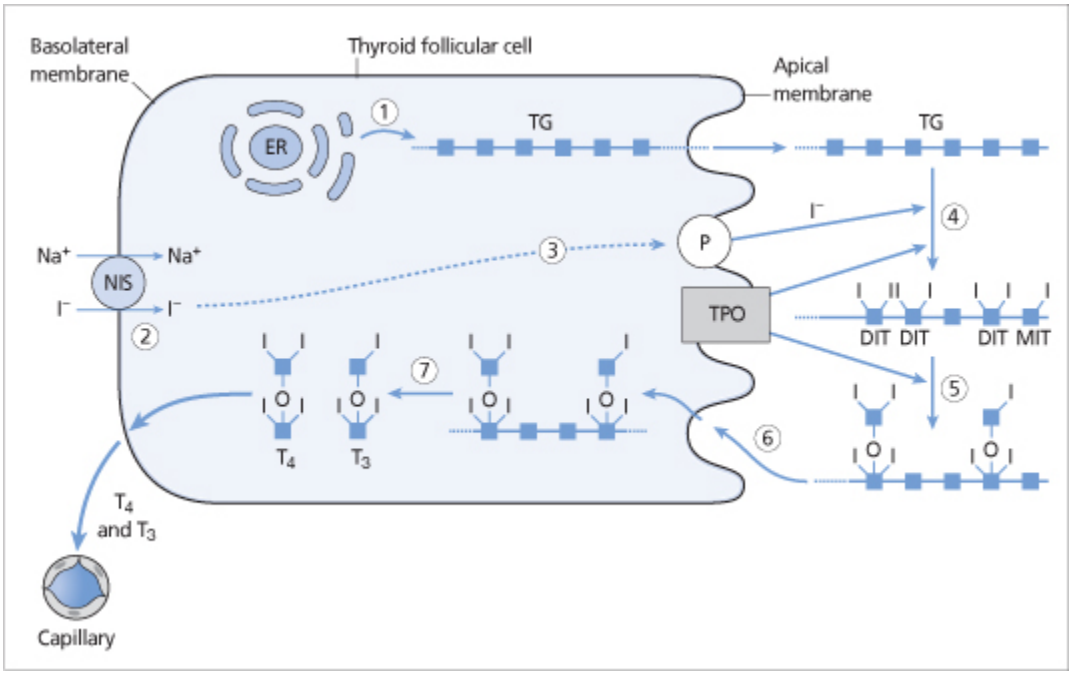
is the predominant deiodinating enzyme in the liver, kidney and thyroid. D2 is the predominant deiodinating enzyme in muscle, brain, pituitary, skin and placenta. Type 3 deiodinase (D3) catalyzes the conversion of T_3 to reverse T_3 (the inactive metabolite) by 5-deiodination (inner ring deiodination), as shown in Fig. 1.5.

Changes in T_3 concentration may indicate a change in the rate of peripheral conversion and may not be an accurate measure of the change in thyroid hormone production. For example, the rate of T_3 production (by 5′-deiodination of T_4) is reduced in acute illness and starvation.

Total and free T_4 and T_3

Approximately 99.97% of circulating T_4 and 99.7% of circulating T_3 are bound to plasma proteins: *thyroid-binding globulin* (TBG), *transthyretin* (also known as thyroid-binding pre-albumin), albumin and lipoproteins.

Figure 1.4 Steps in thyroid hormone synthesis. (1) Thyroglobulin (TG) is synthesized in the endoplasmic reticulum (ER) in the thyroid follicular cells and is transported into the follicular lumen. The small blue squares represent the amino acid residues comprising TG. (2) Iodide is transported into the follicular cell by the sodium–iodide (Na^+/I^-) symporter (NIS). (3) Iodide diffuses to the apical surface and is transported into the follicular lumen by pendrin (P). (4) Iodide is oxidized and linked to tyrosine residues in TG to form diiodotyrosine (DIT) and monoiodotyrosine (MIT) molecules. (5) Within the TG, T_4 is formed from two DIT molecules, and T_3 is formed from one DIT and one MIT molecule. (6) TG containing T_4 and T_3 is resorbed into the follicular cell by endocytosis. (7) TG is degraded by lysosomal enzymes to release T_4 and T_3 molecules, which move across the basolateral membrane of the follicular cell into the adjacent capillaries. TPO, thyroid peroxidase.



Only the unbound thyroid hormone is available to the tissues. T_3 is less strongly bound and therefore has a more

rapid onset and offset of action. The binding proteins have both storage and buffer functions. They help to maintain the serum free T_4 and T_3 levels within narrow limits, and also ensure continuous and rapid availability of the hormones to the tissues.

Free thyroid hormone concentrations are easier to interpret than total thyroid hormone levels. This is because the level of bound hormone alters with changes in the levels of thyroid-binding proteins, even though free T_4 (and T_3) concentrations do not change and the patient remains euthyroid (Fig. 1.6). Box 1.1 summarizes factors that may alter TBG levels.