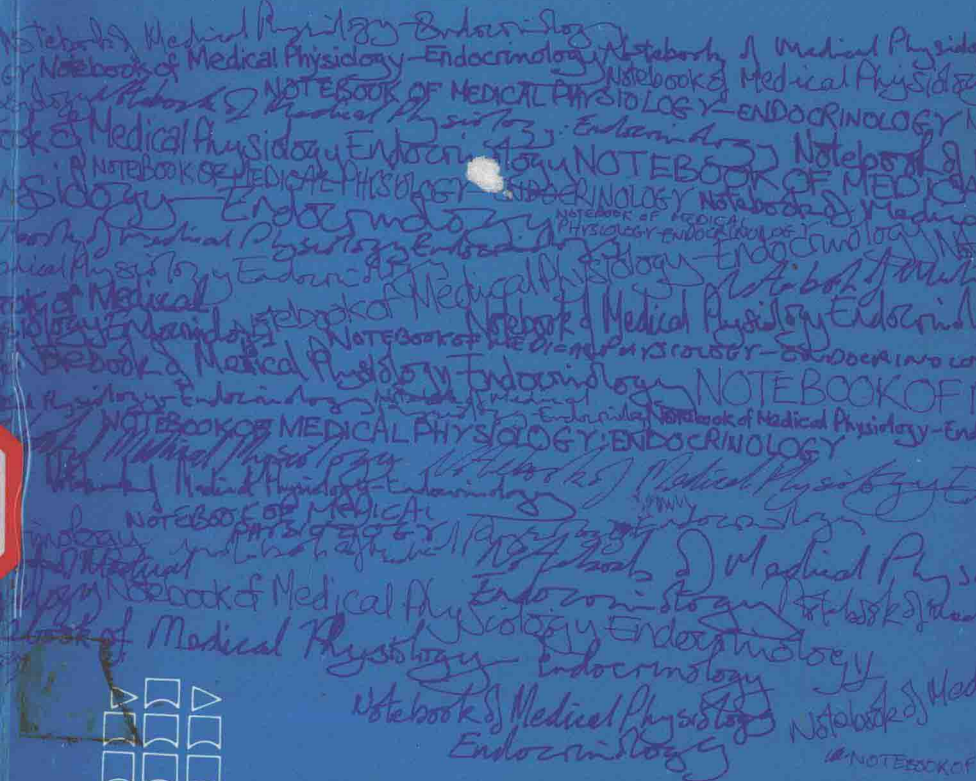
NOTEBOOK OF MEDICAL PHYSIOLOGY

ROSS W. HAWKER

ENDOCRINOLOGY

WITH ASPECTS OF MATERNAL, FETAL & NEONATAL PHYSIOLOGY



CHURCHILL LIVINGSTONE

Notebook of Medical Physiology : Endocrinology

WITH ASPECTS OF MATERNAL, FETAL AND NEONATAL PHYSIOLOGY

A revision text for candidates preparing for examinations in basic medical sciences; including multiple choice questions

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Notebook of Medical Physiology: Endocrinology

To Ailsa

Preface

This is a revision text for students preparing for examinations in medical/surgical science. It is aimed primarily at postgraduates undertaking FRCS, FRACS, FFA, MRCP, FRACP and cognate professional examinations, and secondarily to medical students in both their preclinical and clinical years.

The style is unique and will not please everyone: it is deliberately cryptic and concise and attempts to compress large areas of physiology into readily assimilable facts and concepts with a minimum of description. This is illustrated by the many flow-diagrams and summaries. This didactic approach stems from over 25 years' experience on examination-orientated courses for the FRACS, FRCS, FFA and FRACP.

The self-assessment material in this book has several educational objectives. Firstly, many of the MCQ hopefully are of sufficient quality to merit their use by professional examining bodies, either directly or after further review. Secondly, a considerable number have been constructed to extend the material covered in the text or have some intrinsic teaching quality about them, which makes them unsuitable in their present form for examination purposes. Thirdly, some are intentionally provocative and are designed to prompt discussion by the reader with fellow students or tutors.

1977

R.W.H.

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R.W.H.

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Anatomy

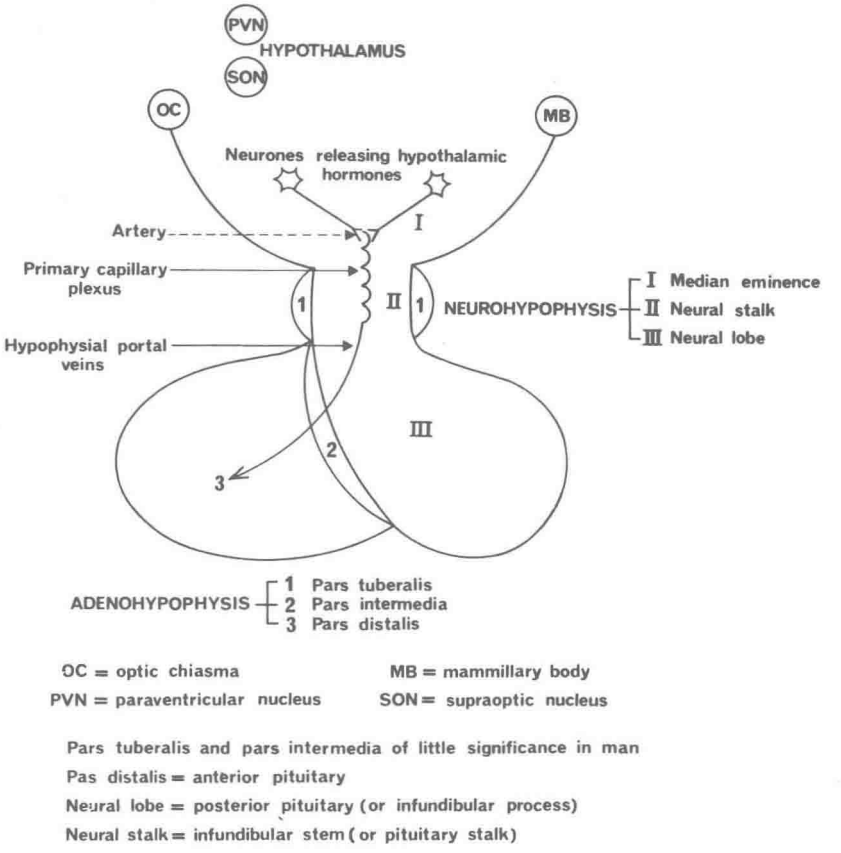


Fig. 1.1 Anatomy of pituitary gland (hypophysis).

Pituitary gland rests in the sella turcica suspended from floor of 3rd ventricle by pituitary stalk and is in close relationship to optic chiasma.

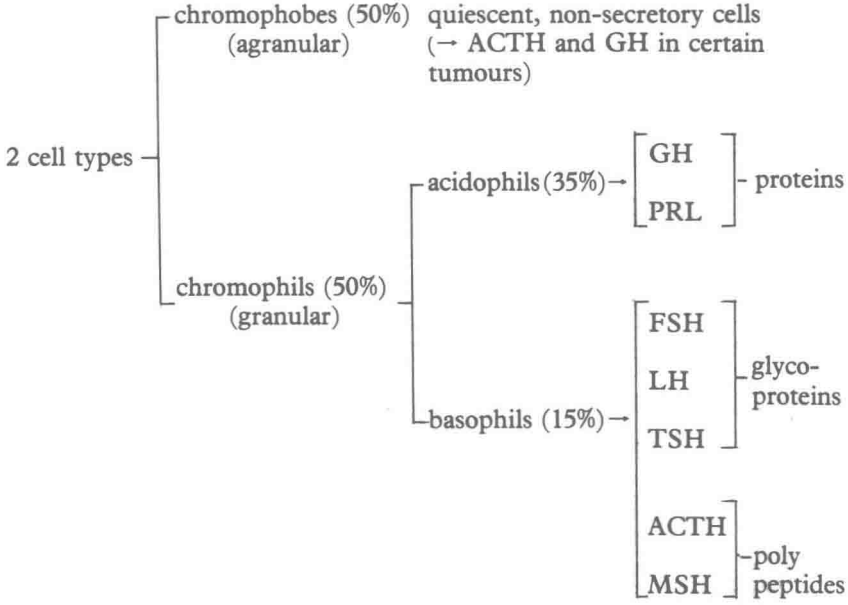
The adenohypophysis is derived from the ectoderm lining the

primitive mouth cavity, and the neurohypophysis from an outgrowth of the hypothalamus.

Hypothalamic-hypophysial portal circulation forms functional link between hypothalamus and anterior pituitary.

Histology

Cell types classified according to arbitrary staining techniques:



Ultrastructural and immunofluorescent studies suggest that each hormone is secreted by a specific cell type:

somatotrophs ⟶ GH

mammotrophs ⟶ PRL

FSH gonadotrophs ⟶ FSH

LH gonadotrophs ⟶ LH

thyrotrophs ⟶ TSH

*corticotrophs ⟶ ACTH, ßMSH and related hormones

*A single cell type, the adrenocortico-melanotroph, in the anterior pituitary appears to secrete both ACTH and ßMSH.

Hormones

1. GH or STH (growth hormone; somatotrophin) protein, MW 22 005 (hGH, human), 191 amino acids.
2. PRL or LTH (prolactin; lactogenic hormone; luteotrophic hormone) protein, MW 23 000 (ovine), 198 amino acids.
3. FSH (follicle-stimulating hormone) glycoprotein, MW 25 000 to 30 000 (hFSH, human).
4. LH (luteinising hormone); ICSH (interstitial cell-stimulating hormone) glycoprotein, MW 26 000 (hLH, human).
5. TSH (thyroid-stimulating hormone; thyrotrophin) glycoprotein, MW ~28 000 (hTSH, human), 209 amino acids.
6. ACTH (adrenocorticotrophic hormone) polypeptide, MW 4541 (hACTH, human), 39 amino acids.
7. MSH (melanocyte-stimulating hormone) polypeptide, MW 2661 (human βMSH), 22 amino acids.

Hormone biosynthesis occurs in ribosomes of rough endoplasmic reticulum; granules are packaged by Golgi apparatus and then secreted by reverse pinocytosis into the blood. Lysosomal enzymes destroy unwanted granules.

The glycoprotein hormones (FSH, LH, TSH and placental HCG) have similar α subunits and different β subunits—these impart hormonal specificity. The α and β subunits of FSH and LH have been detected in plasma in pregnancy and in postmenopausal women, but their biological significance is unknown.

Hypothalamus–anterior pituitary relationships

Until recently it was thought that specific areas in the hypothalamus modulate the release of specific anterior pituitary hormones, but the specificity of these relationships in man is now being questioned.

The nervous pathways into these hypothalamic 'centres' have not been clearly defined, and the chemical mediators at the afferent synapses may be any of a number of substances known to be present locally, viz. acetylcholine (Ach), noradrenaline (NA), dopamine (DA), serotonin (5HT), substance P, and histamine.

The 'centres' consist of diffuse overlapping networks of neurones and each 'centre' regulates the secretion of one or more anterior pituitary hormone by the release of a hypothalamic hormone (neurohormone) into the primary capillary plexus in the median eminence. The releasing factor (or inhibitory factor) is conveyed to the anterior pituitary via the portal system of vessels where it influences the secretion of one or more hormones.

The postulated hypothalamic hormones are:

GRF (GH-releasing factor)

GIF (GH-inhibitory factor; somatostatin)

PIF (PRL-inhibitory factor)

PRF (PRL-releasing factor)

FRF (FSH-releasing factor)
LRF (LH-releasing factor)
} a single substance, gonadotrophin releasing hormone; GRH.

TRF (TSH-releasing factor)

CRF (Corticotrophin- (ACTH-) releasing factor)

Synonyms: 'Factor' and 'hormone' are now commonly used interchangeably in these names. A systematic nomenclature is being introduced in which releasing factors have names ending in '-liberin' (e.g. TRF=thyroliberin) and inhibitory factors, in '-statin' (e.g. GIF=somatostatin). Note that this nomenclature applies to hypothalamic hormones, cf. pituitary hormones' systematic names end in '-trophin' (e.g. TSH=thyrotrophin).

The action of hypothalamic hormones on anterior pituitary cells is probably mediated by adenyl cyclase systems.

These hypothalamic hormones have multiple actions on the anterior pituitary and they are not specific in their actions, e.g. TRF stimulates the secretion of TSH, PRL and sometimes GH (in acromegalics); LRF releases both LH and FSH; and GIF inhibits secretion of GH, TSH and PRL. GH release is stimulated by GRF (probably different from TRF), and is inhibited by GIF; and PRL is stimulated by TRF (and probably by PRF) and tonically inhibited by PIF. A secreting cell in the anterior pituitary thus appears to have more than one type of receptor e.g. cells secreting PRL have PIF receptors and TRF receptors.

When transplanted to a heterotopic site (e.g. under renal capsule) the anterior pituitary loses its cyclicity with respect to secretion of gonadotrophins and its circadian rhythms (e.g. ACTH rhythm), but retains its intrinsic ability to secrete hormones. However, in the transplanted gland the secretion of hormones is greatly reduced with the exception of PRL which is increased.

The gland has a large reserve, and up to 75 per cent may be destroyed before there is significant loss of function.

The hypothalamic hormones are thought to be small peptides: TRF is a tripeptide amide; FRF (LRF) is a decapeptide amide; and GIF is a cyclic tetradecapeptide. Some have been synthesised.

Synthetic analogues of hypothalamic hormones which could act as antagonists are being investigated e.g. an analogue of FRF which would

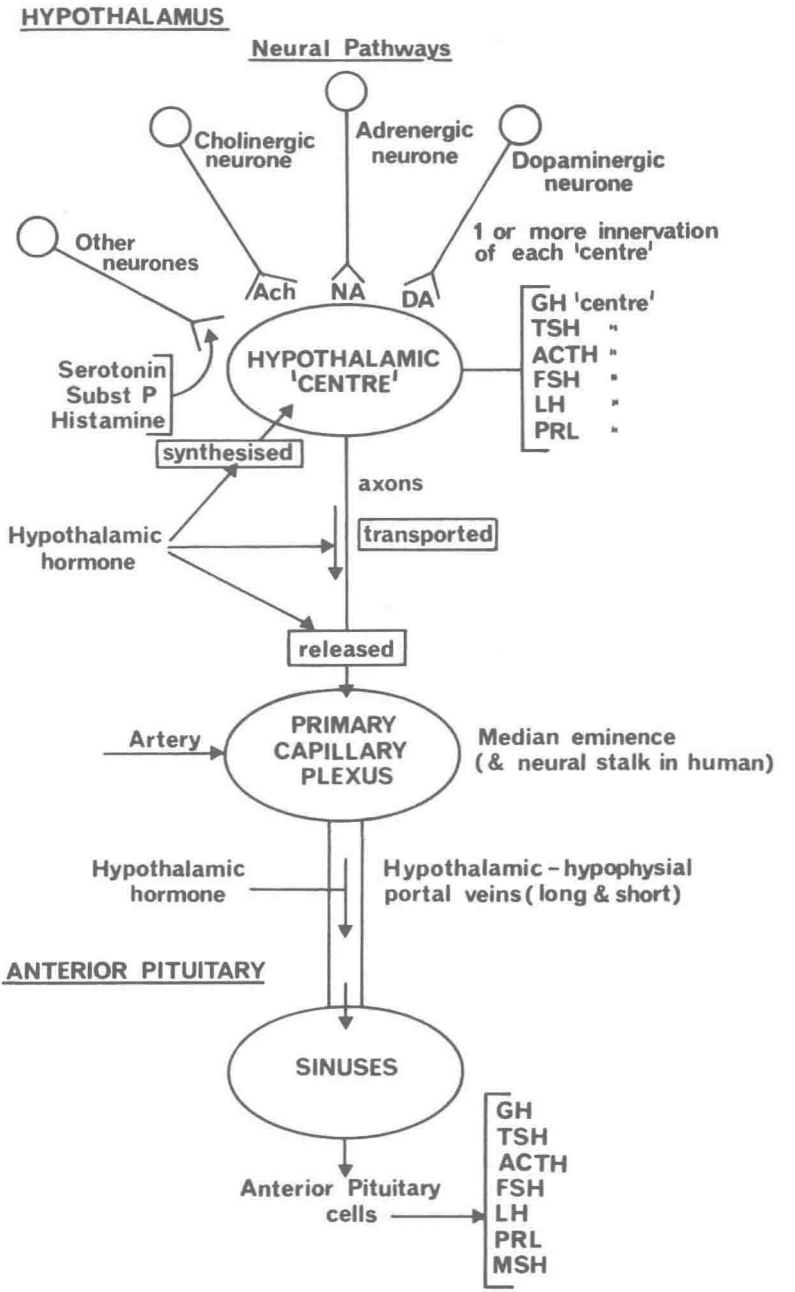


Fig. 1.2 Hypothalamus–anterior pituitary relationship.

act on the gonadotrophs and inhibit the release of FSH and LH could have a contraceptive role in man.

TRF is commercially available and is used as a test of pituitary function.

Somatostatin (GIF) decreases GH release, lowers plasma GH in acromegaly, flattens GH response to hypoglycaemia and lowers insulin secretion. In diabetes mellitus, somatostatin decreases plasma glucose by lowering glucagon secretion.

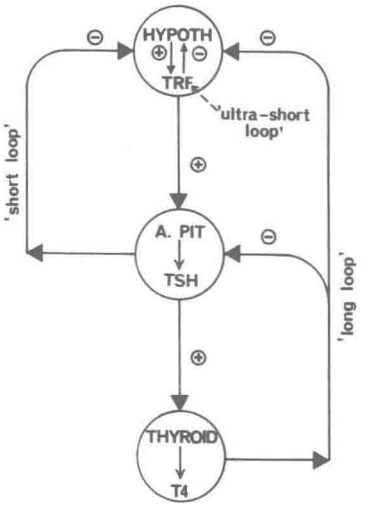


Fig. 1.3 Hypothalamus–anterior pituitary target gland servo-system, e.g. control of thyroid secretion.

Target gland hormone exerts negative feedback control over production of anterior pituitary hormone by direct action on anterior pituitary and indirectly through hypothalamus. The degree of this 'long loop' regulation varies with hormone systems. 'Short loop' and 'ultra-short loop' servo-systems are also thought to exist, but the mechanisms are not clear.

Mechanisms of hormone action

The first step in the modulation of tissue activity is the combination of hormone with a receptor in or on the target cell. Receptors for protein, polypeptide hormones and neurotransmitters are located at the cell membrane. Receptors for steroid hormones are generally intracellular (though the receptor sites for glucocorticoids have not been located).

The adenyl cyclase system mediates the actions of many hormones. The hormonal specificity is conferred by specific receptor sites unique to each target tissue while the catalytic component of the system is very similar in all the target tissues. The following hormones are currently believed to exert their actions by this system; ACTH (adrenal cortex, adipose cells), TSH (thyroid), LH and HCG (the receptor site in Leydig cells of the testis and in cells of the corpus luteum cannot distinguish between the two hormones), FSH (tubule cells of testis and stromal-granulosal cells of the ovary), vasopressin (kidney), calcitonin (kidney), parathormone (kidney), glucagon (liver and adipose cells), secretin (adipose cells), some prostaglandins (stimulate or inhibit cyclase activity in many tissues), adrenaline (ß-adrenergic actions on heart, liver, adipose cells and probably other ß-adrenergic actions).

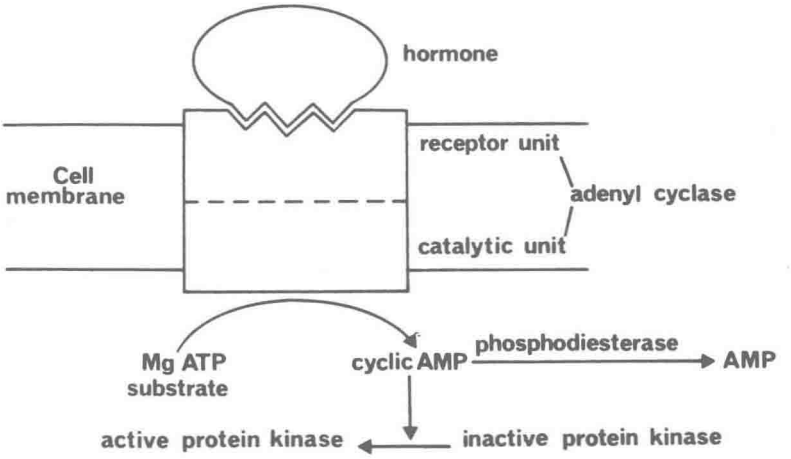


Fig. 1.4 Adenyl cyclase system.

The intracellular second messenger, cyclic AMP formed in response to stimulation of the adenyl cyclase activates protein kinases by binding to the repressor subunit of the kinase causing its dissociation and unmasking the active enzyme. Protein kinases catalyse the phosphorylation of metabolic enzymes, other protein kinases or genetic repressors, thus controlling biochemical activities.

The mechanisms of action of other hormones and neurotransmitters which act on the plasma membrane by mechanisms other than adenyl cyclase activation, are not known, but are thought in many cases to involve changes in membrane permeability. Sex hormones and mineralocorticoids (steroids) combine with intracellular receptors which control gene repression/expression.

Functions of growth hormone

Human growth hormone (hGH), MW 22 005, consists of 191 amino acids with 2 disulphide bridges, and has been synthesised. Species specific (only human and primate GH active in man; other species GH is metabolically inactive in man and evokes immune response). Secretion rate 4 mg/day; level fluctuates between 0 to 30 ng/ml plasma (children and adults; higher in newborn) $t_{1/2}$ 20 minutes.

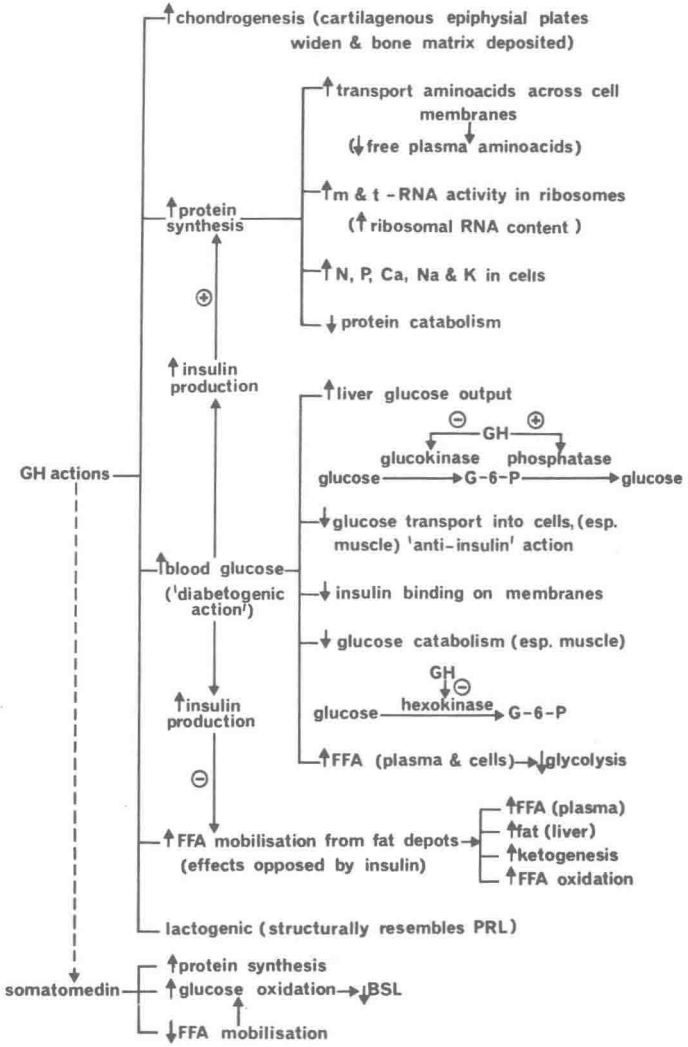


Fig. 1.5 Actions of growth hormone.