ACTH and TSH

1. Adrenocorticotrophic hormone

ACTH is a short peptide of 39 amino acids. Residues 1–24 are highly conserved and confer full activity, such that synthetic ACTH (1–24) is used clinically to test adrenocortical function. ACTH comes from the *proopiomelanocortin* gene (*POMC*), which encodes the POMC protein that is cleaved enzymatically into many potential products (Figure 5.11). These include several forms of melanocyte-stimulating hormone (MSH) and β-endorphin with morphine like activities that may inhibit pain signals to the brain. The enzyme that cleaves POMC to yield ACTH is called prohormone convertase 1/3 (officially abbreviated as PCSK1).

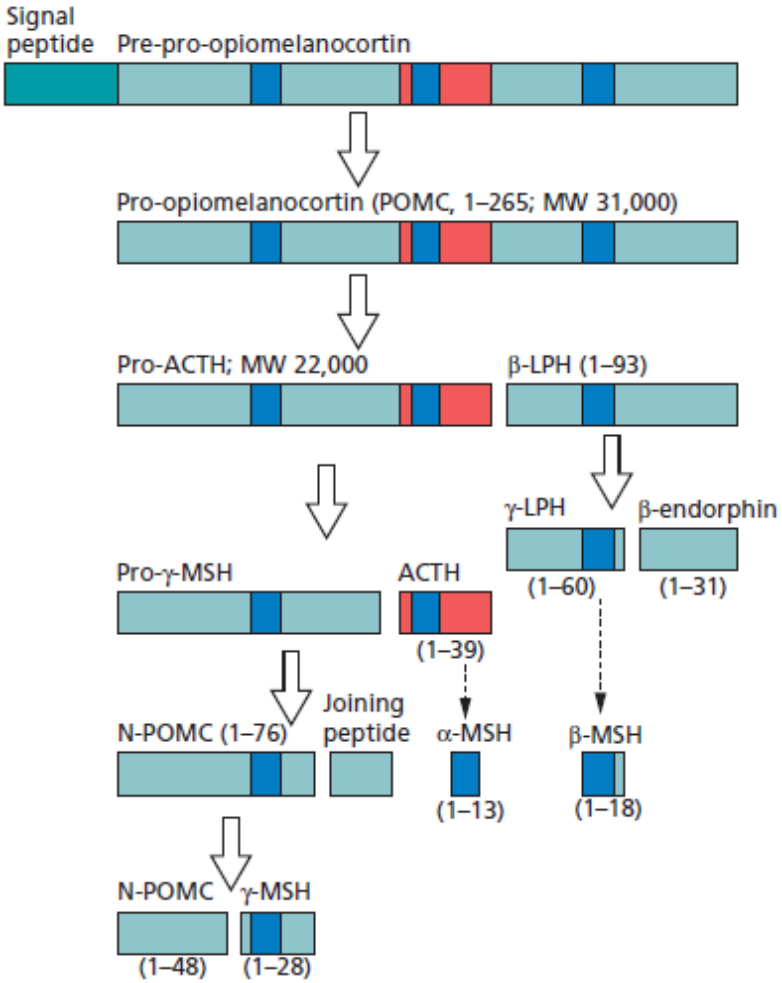

Figure1: The cleavage of proopiomelanocortin (POMC). Adrenocorticotrophic hormone (ACTH) prior to and after cleavage is shown in red. Dark blue areas represent different forms of melanocyte-stimulating hormone (MSH). The number of amino acids in each peptide unit is

shown in parentheses. LPH, lipotrophic hormone; N-POMC, the amino-terminal sequence of POMC. MW, molecular weight in kilodaltons.

Effects and mechanism of action

The major clinical action of ACTH is at the adrenal cortex, where it stimulates several of the enzymatic reactions that convert cholesterol to either cortisol or adrenal sex steroid precursors. The hormone acts on the adrenocortical cell surface via a specific G-protein–coupled receptor, the type 2 melanocortin receptor (MC2R), to increase intracellular levels of cAMP. ACTH also binds the MC1R in the skin to cause pigmentation; a feature that acts as a surrogate marker of corticotroph overactivity in adrenocortical insufficiency. The cleavage of POMC by PC1/3 to generate ACTH is also important in hypothalamic neurons as its failure is a rare monogenic cause of obesity.

Regulation of production

ACTH production is stimulated by CRH from the hypothalamus and inhibited by cortisol from the adrenal cortex in a negative feedback loop (Figure 2). Vasopressin potentiates CRH action and may be particularly important during fetal life. Like PRL and GH, ACTH (and consequently cortisol) rises with stress, mediated by neural inputs from other parts of the brain. This includes stress from hypoglycaemia, such that insulin administration to lower serum glucose is a clinical test of corticotroph function and potential ACTH.

Clinical disorders

Excess ACTH and Cushing disease

An excess of cortisol is called Cushing syndrome. When secondary to too much ACTH from a corticotroph adenoma, the disorder is called Cushing *disease*, after Harvey Cushing who described the original disorder. The corticotroph overactivity stimulates adrenal cortices bilaterally, which become enlarged, and cortisol increases to pathological levels. Clinically, the challenge is to recognize and diagnose glucocorticoid excess (i.e. Cushing syndrome); then to decipher whether the source is adrenal in origin or due to too much ACTH from either the anterior pituitary (Cushing disease) or secreted ectopically from rare tumours, such as small cell carcinoma of the lung.

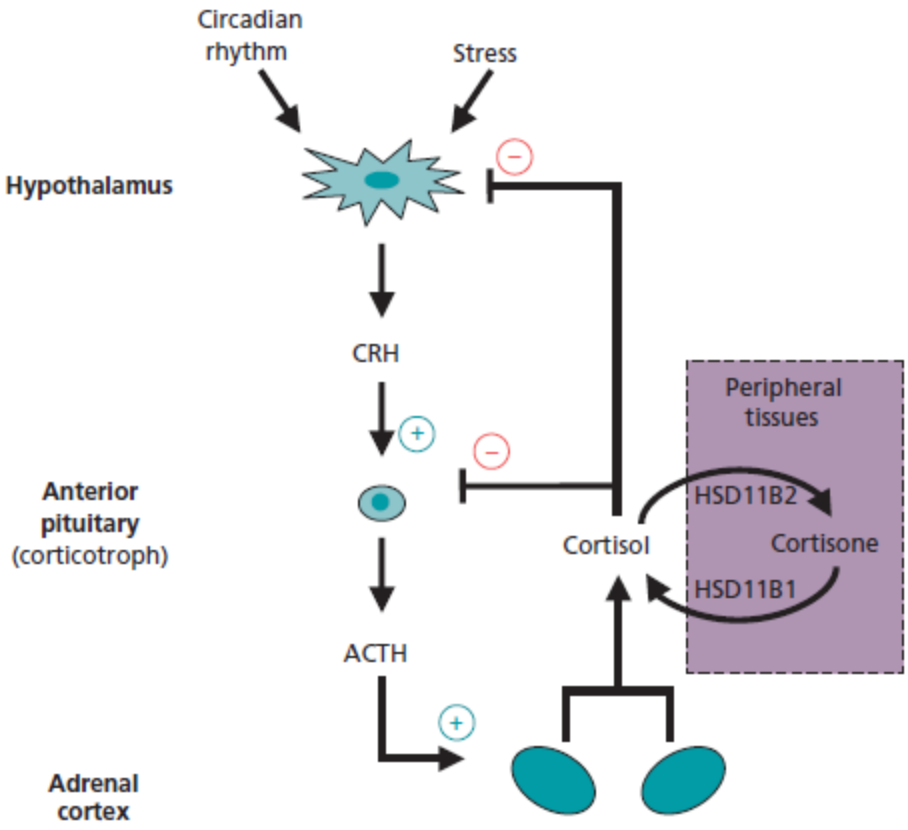

Figure 2: The hypothalamic–anterior pituitary– adrenal axis. Higher brain function (e.g. circadian rhythm and stress) influences corticotrophin-releasing hormone (CRH) synthesis and release, which acts on the corticotroph of the anterior pituitary to make adrenocorticotrophic hormone (ACTH). Both CRH and ACTH are subject to negative feedback by cortisol, the levels of which are influenced in the periphery and in target cells by the balance of 11β- hydroxysteroid dehydrogenase (HSD11B) activity

ACTH deficiency

In ACTH deficiency, biosynthesis of cortisol (and sex steroid precursors) by the adrenal cortex is lost, causing secondary hypoadrenalism. ACTH deficiency for longer than a few months leads to atrophy of the adrenal cortex, which can also be revealed by an inadequate cortisol response to synthetic ACTH(1–24).

2. Thyroid-stimulating hormone

TSH is a glycoprotein composed of two subunits (α and β). The α-subunit is shared by TSH, LH and FSH, with hormone specificity conferred by different, distinctive β-subunits. TSH is synthesized in the thyrotrophs, which constitute ~10% of the cells in the anterior pituitary.

Effects and mechanism of action

TSH is the major physiological regulator of the thyroid gland, stimulating the biosynthesis and secretion of thyroid hormones. The hormone acts on the thyroid follicular cell surface via its specific cell-surface G-protein–coupled receptor to increase intracellular cAMP levels.

Regulation of production

TSH production is stimulated by TRH and acts to stimulate the biosynthesis and release of thyroid hormones – thyroxine (T4) and tri-iodothyronine (T3). Basal TSH secretion depends on tonic TRH release; rare hypothalamic lesions or transection of the pituitary stalk result in TSH deficiency and subsequent hypothyroidism. Negative feedback by thyroid hormone at the anterior pituitary decreases the effectiveness of TRH, in part by reducing TRH receptor number on the cell surface of the thyrotrophs. Somatostatin also inhibits TSH secretion from the anterior pituitary.

Clinical disorders

Excess TSH

Excess TSH is almost always a normal compensation to thyroid underactivity and is used as a screen for hypothyroidism in newborn babies. Tumours that secrete TSH (‘TSHomas’) are very rare. They are usually sporadic macroadenomas and present with hyperthyroidism with inappropriately detectable TSH. The serum α-subunit is usually raised. The differential diagnosis is thyroid hormone resistance syndrome as a result of mutations in the thyroid hormone receptor. The latter condition is usually inherited and may be identified by the family history and genetic testing.

TSH deficiency

Any condition resulting in hypopituitarism can cause TSH deficiency and clinical hypothyroidism.