15.6.1.4: Hormones of the Pituitary

The pituitary gland is a pea-sized structure located at the base of the brain. In humans, it consists of two lobes: the Anterior Lobe and the Posterior Lobe.

Hormones of the Anterior Lobe

The anterior lobe contains six types of secretory cells, all but one of which are specialized to secrete only one of the anterior lobe hormones. All of them secrete their hormone in response to hormones reaching them from the hypothalamus of the brain.

**Thyroid Stimulating Hormone (TSH)**

TSH (also known as thyrotropin) is a glycoprotein consisting of a beta chain of 118 amino acids and an alpha chain of 92 amino acids. The alpha chain is identical to that found in two other pituitary hormones, FSH and LH as well as in the hormone chorionic gonadotropin. Thus it is its beta chain that gives TSH its unique properties. The secretion of TSH is stimulated by the arrival of thyrotropin releasing hormone (TRH) from the hypothalamus and is inhibited by the arrival of somatostatin from the hypothalamus.

As its name suggests, TSH stimulates the thyroid gland to secrete its hormone thyroxine (T4). It does this by binding to transmembrane G-protein-coupled receptors (GPCRs) on the surface of the cells of the thyroid. Some people develop antibodies against their own TSH receptors. When these bind the receptors, they "fool" the cell into making more T4 causing hyperthyroidism. The condition is called *thyrotoxicosis* or *Graves' disease*.

Hormone deficiencies
A deficiency of TSH causes hypothyroidism: inadequate levels of T\(_4\) (and thus of T\(_3\)). Physicians occasionally encounter patients who are homozygous for mutant TSH receptors or mutant TRH receptors. In either case, they suffer from hypothyroidism. A deficiency of TSH, or mutant TSH receptors, have also been implicated as a cause of osteoporosis. Mice, whose TSH receptors have been knocked out, develop increased numbers of bone-reabsorbing osteoclasts.

**Follicle-Stimulating Hormone (FSH)**

FSH is a heterodimeric glycoprotein consisting of the same alpha chain found in TSH (and LH) and a beta chain of 118 amino acids, which gives it its unique properties. Synthesis and release of FSH is triggered by the arrival from the hypothalamus of gonadotropin-releasing hormone (GnRH). The effect of FSH depends on one's sex. In sexually-mature females, FSH (assisted by LH) acts on the follicle to stimulate it to release estrogens. FSH produced by recombinant DNA technology (Gonal-f®) is available to promote ovulation in women planning to undergo *in vitro* fertilization (IVF) and other forms of assisted reproductive technology. In sexually-mature males, FSH acts on spermatogonia stimulating (with the aid of testosterone) the production of sperm.

**Luteinizing Hormone (LH)**

LH is synthesized within the same pituitary cells as FSH and under the same stimulus (GnRH). It is also a heterodimeric glycoprotein consisting of the same 92-amino acid alpha subunit found in FSH and TSH (as well as in chorionic gonadotropin) and a beta chain of 121 amino acids that is responsible for its properties.

The effects of LH also depend on sex. In sexually-mature females, a surge of LH triggers the completion of meiosis I of the egg and its release (ovulation) in the middle of the menstrual cycle; LH also stimulates the now-empty follicle to develop into the corpus luteum, which secretes progesterone during the latter half of the menstrual cycle. Women with a severe LH deficiency can now be treated with human LH (Luveris®) produced by recombinant DNA technology. LH in males acts on the interstitial cells (also known as Leydig cells) of the testes stimulating them to synthesize and secrete the male sex hormone, testosterone. LH in males is also known as interstitial cell stimulating hormone (ICSH).

**Prolactin (PRL)**

Prolactin is a protein of 198 amino acids. During pregnancy it helps in the preparation of the breasts for future milk production. After birth, prolactin promotes the synthesis of milk. Prolactin secretion is stimulated by TRH and repressed by estrogens and dopamine. In pregnant mice, prolactin stimulates the growth of new neurons in the olfactory center of the brain.

**Growth Hormone (GH)**

Human growth hormone (HGH; also called somatotropin) is a protein of 191 amino acids. The GH-secreting cells are stimulated to synthesize and release GH by the intermittent arrival of growth hormone releasing hormone (GHRH) from the hypothalamus. GH promotes body growth by:

- binding to receptors on the surface of liver cells.
- This stimulates them to release insulin-like growth factor-1 (IGF-1; also known as somatomedin)
- IGF-1 acts directly on the ends of the long bones promoting their growth

Things that can go wrong:
• In childhood,
  ◦ hyposecretion of GH produces a short but normally-proportioned body.
  ◦ Growth retardation can also result from an inability to respond to GH. This can be caused by inheriting two
    mutant genes encoding the receptors for
    • GHRH or
    • GH (causing Laron syndrome, a form of dwarfism) or
    • homozygosity for a disabling mutation in STAT5b, which is part of the "downstream" signaling process
      after GH binds its receptor.
  ◦ hypersecretion leads to gigantism
• In adults, a hypersecretion of GH or GHRH leads to acromegaly.

Hormone-replacement therapy

GH from domestic mammals like cows and pigs does not work in humans. So for many years, the only source of GH for
therapy was that extracted from the glands of human cadavers. But this supply was shut off when several patients died
from a rare neurological disease attributed to contaminated glands. Now, thanks to recombinant DNA technology,
recombinant human GH (rHGH) is available. While a benefit to patients suffering from GH deficiency or the short stature
associated with Turner syndrome, there has also been pressure to use it to stimulate growth in youngsters who have no
deficiency but whose parents want them to grow up tall. So, in the summer of 2003, the U.S. FDA approved the use of
human growth hormone (HGH) for boys predicted to grow no taller than 5’3” and for girls, 4’11” even though otherwise
perfectly healthy.

ACTH — the adrenocorticotropic hormone

ACTH is a peptide of 39 amino acids. It is cut from a larger precursor proopiomelanocortin (POMC). ACTH acts on the
cells of the adrenal cortex, stimulating them to produce
  • glucocorticoids, like cortisol
  • mineralocorticoids, like aldosterone
  • androgens (male sex hormones, like testosterone)
  • In the fetus, ACTH stimulates the adrenal cortex to synthesize a precursor of estrogen called
dehydroepiandrosterone sulfate (DHEA-S) which helps prepare the mother for giving birth.

Production of ACTH depends on the intermittent arrival of corticotropin-releasing hormone (CRH) from the
hypothalamus. Hypersecretion of ACTH is a frequent cause of Cushing's syndrome.

Alpha Melanocyte-Stimulating Hormone (α-MSH )

Alpha MSH is also a cleavage product of proopiomelanocortin (POMC). In fact, α-MSH is identical to the first 13 amino
acids at the amino terminal of ACTH. MSH is discussed in a separate page.

The posterior lobe of the pituitary releases two hormones — both synthesized in the hypothalamus — vasopressin
and oxytocin into the circulation.
**Vasopressin**

Vasopressin is a peptide of 9 amino acids (Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly). It is also known as arginine vasopressin (AVP) and the antidiuretic hormone (ADH). Vasopressin acts on the collecting ducts of the kidney to facilitate the reabsorption of water into the blood. Thus it acts to reduce the volume of urine formed (giving it its name of antidiuretic hormone). A deficiency of vasopressin or inheritance of mutant genes for its receptor (called V2) leads to excessive loss of urine, a condition known as diabetes insipidus. The most severely-afflicted patients may urinate as much as 30 liters (almost 8 gallons!) of urine each day. The disease is accompanied by terrible thirst, and patients must continually drink water to avoid dangerous dehydration.

Another type of receptor for vasopressin (designated V1a) is found in the brain, e.g., in voles and mice (rodents) and in primates like monkeys and humans.

- Male prairie voles (*Microtus pinetorum*) and marmoset monkeys have high levels of the V1a receptor in their brains, tend to be monogamous, and help with care of their young.
- Male meadow voles (*Microtus montanus*) and rhesus monkeys have lower levels of the V1a receptor in their brains, are promiscuous, and give little or no help with the care of their young.

Meadow voles whose brains have been injected with a vector causing increased expression of the V1a receptor become more like prairie voles in their behavior. (See Lim, M. M. *et al.*, Nature, 17 June 2004.)

The level of expression of the V1a receptor gene is controlled by a "microsatellite" region upstream (5') of the ORF. This region contains from 178 to 190 copies of a repeated tetranucleotide (e.g., CAGA). Prairie voles have more copies of the repeat than meadow voles, and they express higher levels of the receptor in the parts of the brain associated with these behaviors. A similar microsatellite region is present in the pygmy chimpanzee or bonobo (*Pan paniscus*) but is much shorter in the less-affectionate common chimpanzee (*Pan troglodytes*).

**Vasopressin and the Circadian Clock**

Mice are nocturnal and become active at the start of the night. This is a circadian rhythm that persists for a time even after the lights in the lab are turned off each day 8 hours sooner (like arriving in London after a flight from Los Angeles, California). Only after 8–10 days do the mice overcome their "jet lag", adjusting to the new dark-light schedule. (It also takes us about one day to reset our circadian rhythms for each hour that our day-night schedule is shifted.)

It turns out that arginine vasopressin, acting on the suprachiasmatic nucleus (SCN), plays a role in this resistance to resetting their circadian clock. Mice with their genes for the V1a and V1b receptors knocked out adjust much more quickly (2–4 days) to the change. What evolutionary advantage this resistance to resetting the circadian clock confers is not clear, but understanding the mechanism raises the possibility of using drugs to speed getting over jet lag and also to help those whose work shifts are periodically altered. (Read about this work in Yamaguchi, Y., *et al.* in the 4 October 2013 issue of Science.)

**Oxytocin**

Oxytocin is a peptide of 9 amino acids (Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly). It acts on certain smooth muscles by stimulating contractions of the uterus at the time of birth and stimulating release of milk when the baby begins to suckle. Oxytocin is often given to prospective mothers to hasten birth.
In rodents, oxytocin also acts on the nucleus *accumbens* and *amygdala* in the brain where it enhances bonding between males and females after they have mated and bonding between a mother and her newborn. In mice, oxytocin acts on *striated muscle* stem cells to promote repair after they have been injured. In humans, oxytocin increases the level of one’s trust in other people.

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