

PHARMACOLOGY

Pharmacology of Endocrine System: Pituitary Hormones

Dr Pramod Kumari Mediratta
Professor
Dept. of Pharmacology
University College of Medical Sciences
G.T.B. Hospital Campus
Shahdara
Delhi – 110095

(15-5-2007)

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Keywords

pituitary, anterior, hormone, somatotropin, prolactin, gonadotropin, GnRH analogues, pegvisomant

Anterior Pituitary Hormones

The growth, metabolism and reproduction are regulated by the neuroendocrine system located in the hypothalamus and pituitary gland. The pituitary gland weighs 0.6g and consists of two parts: anterior part (adenohypophysis) and posterior part (neurohypophysis). The pituitary is connected with the hypothalamus by means of the portal system which regulates its action by the 'releasing' and 'release inhibiting' hormones.

The neurosecretory fibres take the posterior lobe hormones synthesized in the nerve cell bodies in supraoptic and paraventricular nuclei of hypothalamus to the posterior lobe from where they are released into the circulation. These hormones are oxytocin and antidiuretic hormone (ADH, vasopressin).

The anterior pituitary hormones are classified into:-

- a) Somatotropes : growth hormone (GH) and prolactin (Prl)
- b) Glycoprotein hormones : thyrotropin (TSH), luteinising hormone (LH), follicle stimulating hormone (FSH), and human chorionic gonadotropin (hCG) which is produced by the placenta
- c) Pro opiomelanocortin (POMC) derived peptides: corticotropin (ACTH), α and β melanocyte stimulating hormone (α -MSH, β -MSH)

Growth Hormone (Somatotropin, GH)

Somatotropin is a 191 amino acid peptide hormone that has two disulfide bonds. It is not glycosylated. The half life of endogenous GH is 20-25 minutes and it is cleared by the liver. The half life of protein bound GH is much more (about 10 times that of free GH) so that no acute fluctuations occur because of pulsatile secretion of GH. Cadaveric pituitary derived GH is not used because of development of Creutzfeldt Jacob disease in recipients. Animal GH is ineffective in humans and now, recombinant growth hormone (rhGH) is most frequently used. Somatotropin and somatrem are the two preparations of rhGH. Somatotropin has 191 amino acids while somatrem has an additional methionine group at the amino terminal end.

Regulation of GH secretion: The secretion of GH in humans varies throughout their life; it is higher in children reaching a maximum at puberty and then decreases in adults. The secretion of GH from pituitary is controlled by growth hormone releasing hormone (GHRH) and growth hormone inhibiting hormone (GHRH) both of which are secreted by the hypothalamus. GH secretion is increased by fasting, hypoglycemia, stress, exercise and α adrenergic agonists while it is decreased by free fatty acids, insulin like growth factor 1 (IGF 1), β adrenergic agonists, GH itself and dopaminergic agonists. Dopaminergic agonists like bromocriptine increase the release of GH in normal people but ironically decrease the release in acromegalics.

Physiologic Effects: The most important effect of GH is stimulation of longitudinal growth of bones. Bone mineral density increases if given after the cessation of longitudinal growth and epiphyseal closure. It stimulates the growth of almost all tissues and organs in the body. However, it does not regulate the growth of brain and eyes. It increases lipolysis and gluconeogenesis thereby having an anti insulin effect. The anabolic effects of growth hormone are mediated primarily by somatomedins or insulin like growth factors 1 and 2 (IGF 1, IGF 2). Most of IGF 1 is synthesized in the liver. The other effects of GH also include increasing muscle

mass, increasing glomerular filtration rate and even a role in the development of immunity. Excessive GH causes gigantism in children and acromegaly in adults while pituitary dwarfism is the result of decreased GH secretion.

Mechanism of Action: GH produces its effect by interacting with the GH receptor which is a cell surface receptor belonging to the cytokine receptor superfamily. GH receptor has an extracellular ligand binding domain with a membrane spanning region and an intracellular domain which is responsible for mediating signal transduction. One molecule of GH binds to two identical receptor molecules causing dimerization of the receptors. The ligand bound GH receptor does not have a tyrosine kinase activity per se but associate with cytoplasmic tyrosine protein kinases and phosphorylates relevant proteins and ultimately affect gene expression.

Uses

1. **Pituitary dwarfism:** In children having short stature due to GH deficiency, therapy with rhGH results in many children with short stature to achieve normal adult height. It is administered subcutaneously in a dose of 20-40 μ g/ kg once daily in the evening.

The most marked increase in growth occurs during the first two years of therapy. GH administration is continued until further growth stops. Recombinant IGF-1 is also available which can be given subcutaneously to children where there is no deficiency of GH but change in the GH receptors, as a result there is defective production of somatomedins or IGF-1.

2. **Adults with GH deficiency:** It occurs due to damage to the hypothalamus or pituitary by surgery, radiation exposure, infection or trauma. The treatment of such patients with GH results an increase in body mass, bone density, exercise tolerance and a general sense of well being. Treatment is started at a lower dose of 0.2 mg three times a week and gradually increased to a maximum of 0.025 mg/kg/day.

3. **Miscellaneous :** Patients having turner syndrome, X- linked hypophosphatemia, vitamin D resistant rickets etc. also improve on addition of GH in their treatment regimen.

Adverse Effects: Children generally tolerate growth hormone better than adults. Some of the side effects with the use of GH include myalgia, arthralgia, lipodystrophy and pain at the injection site, edema, nausea, headache and hypothyroidism (which may get unmasked and therefore, periodic thyroid function assessment should be done).

Somatostatin (SST, Growth hormone release inhibiting hormone)

It is a 14 amino acid peptide which inhibits growth hormone release. It also inhibits the release of glucagon, insulin and gastrin. The half life of somatostatin is 1-3 minutes. It exists in both 14- and 28- amino acid form. Five subtypes of somatostatin receptors (SSTR 1-5) have been recognized. The somatostatin receptor subtypes 2 and 5 are the most important for the regulation of GH secretion.

Nowadays, somatostatin's analog octreotide is used which has a longer half life, is more specific for the somatostatin receptors (SSTR-2 and SSTR-5). It is administered thrice daily by subcutaneous injection in a dose of 100 μ g. A delayed release long acting preparation

(sandostatin LAR) is now available which is administered intramuscularly once a month. A longer acting somatostatin analogue lanreotide is also available which needs to be given at 10 or 14 day interval. The various indications for the use of somatostatin and its analogs include metastatic carcinoid tumors, acromegaly, WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome, acute variceal bleeding (as it reduces gastric blood flow) and as a diagnostic agent for neuroendocrine tumors.

Adverse effects include abdominal pain, nausea, diarrhea, development of gallstones and vit. B₁₂ deficiency on use for long durations.

Growth Hormone Receptor Antagonists

Pegvisomant is the drug in this category which is used for treating acromegaly. It is a polyethyleneglycol polymer attached to a modified GH molecule which cannot activate GH receptor despite binding to it. It is administered subcutaneously and is known to cause increased serum transaminases. Liver function tests should be done periodically in patients receiving the drug.

Growth Hormone Releasing Hormones (GHRH) and Synthetic Peptides

GHRH released from the arcuate nucleus of the hypothalamus causes the stimulation of synthesis and release of growth hormone from the pituitary. Though GHRH is itself not available commercially but its synthetic peptides having similar actions like sermorelin, hexarelin etc, are presently being used. The primary use of sermorelin is for the treatment of GH deficiency. It is also used diagnostically for the testing of pituitary GH secretory capacity in patients undergoing evaluation for clinical short stature. COX inhibitors, octreotide and steroids alter the response of the diagnostic evaluation. The common side effects include flushing, rash, headache, nausea, chest discomfort and metallic taste.

Prolactin

It is a 199 amino acid peptide hormone synthesized by the lactotropes in the anterior pituitary gland. Its serum levels decline after birth. The hormone level remains elevated in females in comparison to males, rise during pregnancy, peak at term and declines thereafter. It is also secreted in a pulsatile manner. Sleep, stress, exercise and hypoglycemia increase the secretion of prolactin just as they do for growth hormone. Prolactin per se has no therapeutic use.

Regulation of secretion and physiological functions: The hypothalamic regulation of prolactin secretion is predominantly inhibitory and this is mediated by dopamine. So dopamine agonists like bromocriptine, quinagolide (non ergot dopamine agonist), pergolide and cabergoline (both ergot derivatives) decrease prolactin levels whereas dopamine antagonists like classical antipsychotic drugs (chlorpromazine, haloperidol etc), methyl dopa, reserpine cause hyperprolactinemia which may manifest as galactorrhea and hypogonadism. Prolactin is required for the growth and differentiation of ductal and lobuloalveolar epithelium of the breasts during pregnancy and is essential for lactation.

Dopamine Agonists

This group includes bromocriptine, quinagolide, pergolide and cabergoline. The dopamine agonists directly inhibit prolactin release by acting on pituitary and by generating increased

hypothalamic dopamine due to decreased turnover in arcuate nucleus. These agents cause stimulation of growth hormone release in normal subjects but paradoxically cause inhibition of growth hormone release in patients having acromegaly. Bromocriptine has more activity on D₂ receptors than D₁ receptors. Though pergolide is primarily used for treating parkinsonism but its distinct advantage is that it is the cheapest dopamine agonist.

Uses:

1. **Hyperprolactinemia:** caused commonly due to pituitary microadenoma. Though the dopamine agonist benefit galactorrhea and hypogonadism but tumor growth recurs on cessation of therapy.
2. **Lactation suppression:** Bromocriptine is used to suppress lactation in females not desiring to breastfeed or those having stillborn babies to prevent breast engorgement. Quinagolide is also used for cyclical mastodynia.
3. **Acromegaly:** as an adjunct to surgery and irradiation, bromocriptine and other dopamine agonists can be used.
4. **Parkinsonism:** Pergolide and less frequently bromocriptine is used in the management of parkinsonism.

Adverse Effects: Frequent side effects reported with bromocriptine include nausea, headache, vomiting, postural hypotension, psychosis and hallucination. Bromocriptine is started at a lower dose and then the dose increased to minimize the side effects. Gastrointestinal side effects can be circumvented by the intravaginal use of drug. The ergot preparations may cause peripheral vasospasm. These drugs should be avoided in pregnant women.

Gonadotropins

The gonadotropic hormones are so named because of their actions on the gonads and include the luteinizing hormone (LH) and follicle stimulating hormone (FSH). There is another gonadotropin, human chorionic gonadotropin (hCG). This is produced by the placenta and is similar to LH. These hormones contain two distinct subunits, α and β . The α subunits are identical in all of these hormones and β subunits confer specificity of biological actions. Unlike GH and prolactin these hormones are heavily glycosylated.

Regulation of Secretion : A decapeptide called GnRH (gonadotropic releasing hormone) produced by the arcuate nucleus of hypothalamus controls the release of LH and FSH. Though pulsatile release of GnRH causes increased release of LH and FSH, paradoxically sustained administration of GnRH inhibits the gonadotropins release from the pituitary. Inhibins produced by the gonads also directly inhibit FSH secretion without inhibiting the secretion of LH. The differential production of LH and FSH is controlled by the frequency of GnRH pulses. Estradiol and progesterone inhibit both LH and FSH, though the preovulatory increased estrogen levels stimulate LH and FSH secretion paradoxically. Consequently, ovulation occurs secondary to the mid cycle LH surge.

Physiological Function : In females, FSH stimulates the follicular growth and increases the expression of LH receptors on theca and granulosa cells. LH is required both for ovulation and for progesterone synthesis by the corpus luteum.

In males, LH is required for the synthesis of testosterone from leydig cells which in turn is required for gametogenesis and maintenance of secondary sexual characters. FSH stimulates the production of nutrients for the sperm maturation and is required for spermatogenesis. Decreased secretion of gonadotropins result in delayed puberty and sterility in both females and males whereas their increased production causes precocious puberty in young children and polycystic ovaries in adult women.

Mechanism of Action : The actions of LH and FSH are mediated by their interaction with LH and FSH receptors respectively. These are G protein coupled receptors coupled to adenyl cyclase. They activate adenyl cyclase and raise the intracellular level of cyclic AMP. hCG acts on the LH receptors.

Gonadotropin Preparations: The purified extracts of LH and FSH (called menotropins) derived from the urine of post menopausal women have been used clinically though nowadays, recombinant FSH called follitropin alpha and follitropin beta are also available. They are considerably purer but are expensive. A purified form of human FSH called urofollitropin is also one of the options available for the treatment. From this, LH fraction has been removed. A highly purified preparation of FSH is also prepared by immunoconcentration with monoclonal antibodies (Metrodin HP). Since there is no LH preparation currently available so, hCG which has a similar structure is used as a substitute for LH. It is obtained from the urine of pregnant females.

The menotropins have a half life of 2-6 hours and are excreted unchanged in urine. hCG has a half life of 7-8 hours while half life of LH is 30-40 minutes. The purified preparation can be administered subcutaneously, however, relatively less purified preparations are given by intramuscular route of administration.

Uses:

1. **Detection of pregnancy:** Presence of significant amount of hCG in the urine of pregnant women helps in the diagnosis of pregnancy using immuno assay kits which detect the presence of β hCG. Quantative measurement of hCG in plasma is done to assess whether the pregnancy is progressing normally or not. It is also used to detect ectopic pregnancy, hydatiform mole or choriocarcinoma.
2. **Diagnosing diseases of male and female reproductive system:** In these cases, levels of LH and FSH are measured. Whereas LH and FSH are decreased in case of hypogonadotropic hypogonadism, the levels of gonadotropins are increased in primary gonadal failure.
3. **Treatment of female infertility:** Gonadotropins are useful in anovulatory women with hypothalamic or pituitary dysfunction being the cause of hypogonadotropic hypogonadism. They are also used as second line drugs for induction of ovulation on women with polycystic ovarian syndrome who fail to respond to clomiphene citrate.

4. **Treatment of male infertility:** Hypogonadotropic hypogonadism manifests as delayed puberty, oligozoospermia and male infertility. They respond to treatment with the gonadotropins.
5. **Invitro fertilization:** The gonadotropin supplements are used for exact timing ovulation and then using this information to extract the ovum and using it for invitro fertilization.
6. **Cryptorchidism:** In these cases, some cases may respond to gonadotropin treatment if the failure of testicular descent is not due to anatomical blockage. The treatment should be started as early as possible because delayed descent results in defective spermatogenesis and increased risk of cancers in the undescended testes.
7. **AIDS:** Injection of hCG in the lesions of AIDS related Kaposi sarcoma causes regression in some cases.

Adverse Effects: The use of menotropins is associated with the development of ovarian hyper stimulation syndrome characterized by polycystic ovaries, ascites, hydrothorax, dyselectrolytemia, respiratory distress and shock. There is an increased incidence of multiple births with their use. Other adverse effects include precocious puberty, headache, depression and gynecomastia.

Gonadotropin Releasing Hormone (GnRH)

As has been discussed in the regulation of secretion of gonadotropins, GnRH is crucial for the synthesis and release of gonadotropins. It is a decapeptide derived from a precursor peptide molecule. The GnRH used clinically is synthetic GnRH (Gonadorelin). Its analogs like leuprolide, nafarelin, goserelin, buserelin and histrelin are also available. They are administered intramuscularly, subcutaneously, and by nasal or intravenous route. The half lives of GnRH analogs through subcutaneous and intranasal route is about 2.5-3 hour in comparison to GnRH which has a half life of 2-4 minutes. The synthetic analogs are much more potent, have increased affinity for the receptors and are degraded slowly. As has been noted, pulsatile GnRH administration increases the release of LH and FSH whereas continuous GnRH administration inhibits gonadotropin release. GnRH analogues are used to suppress the secretion of gonadotropins.

Uses:

1. **Diagnosis of hypogonadotropic hypogonadism:** After a subcutaneous or intravenous bolus injection of GnRH, the levels of LH are measured. A peak LH response suggests impending puberty whereas an impaired LH response suggests hypogonadotropic hypogonadism.
2. **Treatment of infertility:** Pulsatile therapy with GnRH(gonadorelin acetate) is given with the help of an intravenous pump for the pituitary stimulation and is used for the treatment of infertility caused by hypothalamic hypogonadotropic hypogonadism females. The advantages of gonadotropin therapy include lower risk of multiple pregnancies and decreased need of monitoring plasma estrogen levels. In males, use of GnRH is not preferred because of longer period of administration. This turns out to be more expensive and infusion pump has to be worn continuously.

3. **Suppression of gonadotropin secretion:** The GnRH analogs induce hypogonadism when given continuously and so they are useful in the treatment of several hormonal dependent conditions like prostate and breast cancer, endometriosis, uterine fibroid and precocious puberty. They are also used in invitro fertilization to help in synchronizing the follicular development along with external gonadotropin supplementation.

Adverse Effects: The use of gonadotropins is associated with headache, local swelling at injection site, nausea, flushing and anaphylaxis. The GnRH analogs also cause headache, depression, osteoporosis on long term use, development of ovarian cysts, decreased cysts, hot flushes(in women), pain, neurological symptoms in patients with bone metastasis, generalized weakness and gynecomastia (in men). Rhinitis is a common side effect reported with the use of nasal preparations. The GnRH therapy causes transient increase in sex hormone concentrations initially which can be deleterious in patients undergoing treatment for prostate cancer, uterine fibroid, precocious puberty and infertility. The initial flare of prostate cancer can be prevented with the simultaneous use of anti androgens for 2-4 weeks.

Gonadotropin Releasing Hormone Antagonist (GnRH Antagonist)

Two GnRH antagonists' ganirelix and cetrorelix have been developed which bind to the GnRH receptors without activating them, So, they inhibit the FSH and LH secretion without initial stimulation. They are given subcutaneously and the duration of action is nearly 3-4 days.

Uses:

1. **Invitro fertilization:** Cetrorelix suppresses endogenous gonadotropins while external FSH and LH are given to achieve synchrony in preparation of ova whose induction is done using hCG. It causes less ovarian hyper stimulation.
2. **Gynecological disorders:** Once weekly preparations are given for about 2 months to treat endometriosis and for the management of uterine fibroids; the drug is given on the first day of the menstrual cycle.

Thyrotropin Releasing Hormone (TRH)

TRH is a tripeptide hormone which is found in the paraventricular nuclei of the hypothalamus. It stimulates the pituitary gland to secrete the thyroid stimulating hormone (TSH). TRH is given slowly intravenously. Its half life is about 5 minutes. It also increases prolactin secretion. The levels of TRH can be measured and used to distinguish primary, secondary or tertiary hypothyroidism. In primary (thyroid origin) hyperthyroidism, TSH levels are high and may show an increased response to TRH administration. In secondary(pituitary origin) hypothyroidism, TSH levels are low and they fail to increase even after giving TRH .In tertiary hypothyroidism (due to hypothalamic cause), the serum TSH levels may be normal or low and they may remain low or normal in response to TRH. The only rare use now of TRH is for diagnosing hyperthyroidism or hypothyroidism. The adverse effects include nausea, headache, blood pressure fluctuations and metallic taste.

Thyrotropin (TSH)

It is secreted by the anterior pituitary and stimulates the thyroid to secrete T_3 and T_4 .It is a glycoprotein hormone containing non covalently α and β subunits. Though the alpha subunit of

TSH resembles the alpha subunit of FSH and LH but it is the β subunit which confers it the specificity. A commercial available analog of TSH called recombinant human TSH is used in the detection of metastatic well differentiated carcinoma of the thyroid. Its half life is about 20 hours. TSH is cleared by the kidney and liver. It is given intramuscularly.

Uses:

1. **In thyroid carcinoma:** Thyrotropin can be used for diagnosis as well as treatment of well differentiated thyroid carcinoma alongwith radioactive iodine ^{131}I . After thyroidectomy in patients with well differentiated carcinoma, these patients need follow up with the regular periodic estimation of their TSH, T_3 and T_4 levels.

2. **Diagnosing hypothyroidism:** To distinguish between hypothyroidism caused by primary thyroid disease or pituitary dysfunction.

Adverse Effects: Nausea, headache, hypersensitivity and even hyperthyroidism may occur secondary to the use of thyrotropin.

Corticotropin Releasing Hormone (CRH)

CRH is a 41 amino acid peptide hormone released from the hypothalamus. It is administered intravenously with most of it getting metabolized in the body tissues itself. It causes the release of ACTH from the pituitary. The only use of CRH is to distinguish between Cushing's disease and ectopic ACTH secretion. Sheep CRH is also available which is more potent, has a longer half life and therefore, is more frequently used. Facial flushing is the only known side effect.

Adrenocorticotropin (ACTH)

Human ACTH is a 39 amino acid peptide hormone released from the anterior pituitary. It is derived from a precursor molecule, pro-opiomelanocortin(POMC). Secretion of ACTH is in a circadian rhythm: peak levels are in the early morning and lowest levels are at mid night. Synthetic human ACTH which is less allergic is known as cosyntropin. Half life of ACTH is about 20 minutes. It acts on the adrenal cortex and stimulates it to secrete glucocorticoids, mineralocorticoids and sex steroids. It increases the activity of the enzyme cholesterol esterase which converts cholesterol to pregnenolone. It is also known to improve learning in experimental animals. Excessive ACTH production leads to the development of Cushing's syndrome.

Uses:

1. **Diagnostic use:** Quantitative estimation of ACTH can be done is used to rule out adrenal insufficiency as its levels are increased in primary adrenal insufficiency while they are decreased in the secondary form. It is also used to differentiate between the different forms of congenital adrenal hyperplasia. Cosyntropin is the preparation of choice for diagnostic use.

2. ACTH has been tried in place of direct administration of glucocorticoids but it is more inconvenient and the response is unpredictable.

Adverse Effects: Anaphylaxis, pain and swelling at the injection site and glucocorticoid overproduction occur with the use of ACTH. Sodium retention, acne and hyperandrogenism in women are also seen.

Suggested Reading

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