**GnRH AND THE GONADOTROPINS**

**I. GONADOTROPIN-RELEASING HORMONE (GnRH)**

**IA. OVERVIEW**

Gonadotropin-Releasing Hormone controls release of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), from the anterior pituitary. The two primary therapeutic uses of GnRH agonists are: [1] to mimic effects of GnRH for treatment of infertility; or [2] to block effects of GnRH, via desensitization, in order to inhibit the function of the axis in patients with hormone-dependent disorders.

**IB. REVIEW OF BASIC PHYSIOLOGY**

GnRH is a 10 amino acid peptide derived from a 92 amino acid precursor. It is released from hypothalamic GnRH-synthesizing neurons in a **pulsatile** fashion, at a rate of approximately one pulse per hour. GnRH release is controlled by ‘pacemaker’ neurons located in the anterior mediobasal hypothalamus.

- Pulsatile GnRH release is transiently present in the early neonatal period, damped during early childhood and reinitiated at the time of puberty. The pattern of reinitiation is such that early in puberty GnRH pulses occur mainly at night. Later in puberty and thereafter, hourly GnRH pulses are apparent throughout the day.
- The rate and amplitude of GnRH pulses is under long-loop negative feedback control by steroid hormones.
- Release is enhanced at mid-cycle in females by estrogen, providing a GnRH surge that drives the surges of gonadotropins (especially LH) that mediate ovulation.
- GnRH secretion is inhibited by prolactin. This is responsible for the inhibition of ovulation in nursing mothers. In addition, hyperprolactinemia is an important potential cause of hypogonadotropic hypogonadism and infertility.
- GnRH release is inhibited by stress and vigorous exercise, which can result in amenorrhea.
The major effect of GnRH is to stimulate release of LH and FSH. It is released at the median eminence and transported via the portal circulation to the anterior pituitary, where it acts via a G-protein-coupled receptor, involving activation of phospholipase C and production of diacylglycerol and IP3, to stimulate gonadotropin release and synthesis.

- GnRH exerts a self-priming effect on gonadotropes, such that gonadotropin release is enhanced following a prior application of GnRH. This effect is augmented by estradiol, contributing to the positive feedback effect of E2 at mid-cycle.

**IC. GnRH Pharmacology**

Synthetic human GnRH and four long-acting GnRH agonists are available for use in the United States. Early GnRH antagonists, although potent inhibitors of gonadotropin secretion also had the adverse effect of causing mast cell degranulation; second generation antagonists (e.g. ganirelix) without those side effects are in clinical trials, but have not yet been approved for use.

**IC1. GnRH and Synthetic Analogs**

Most GnRH agonists substitute a hydrophobic D-amino acid for glycine at position 6 and replace the glycine-amide with N-ethylamide at position 10. These substitutions result in slower clearance and increased potency because of increased affinity for GnRH receptors, greater binding to plasma proteins and reduced proteolytic cleavage.
IC2. Therapeutic Uses of GnRH

Pulsatile delivery of GnRH, mimicking the normal endogenous patterns, stimulates gonadotropin release, whereas continuous application inhibits gonadotropin secretion by a desensitization process. This forms the basis for the therapeutic use of GnRH agonists to either enhance (when administered in pulsatile fashion) or suppress (when delivered continuously) gonadotropin secretion.

To enhance gonadotropin secretion (e.g. assisted fertility)

In patients with GnRH deficiency, pulsatile administration of gonadorelin hydrochloride, the short-acting synthetic human GnRH, can be used to stimulate gonadotropin secretion and induce ovulation and spermatogenesis.

- The regimen for administering these agents (dose and timing of the pulses) to treat infertility is complex and requires optimization for each individual. A portable infusion pump is provided in a kit (LUTREPUCE) for pulsatile intravenous delivery of gonadorelin.

To suppress gonadotropin secretion (e.g. precocious puberty, hormone-dependent neoplasias, endometriosis)

Chronic administration of a long-acting GnRH agonists will suppress gonadotropin secretion. At least two weeks of treatment are necessary for essentially complete inhibition of gonadotropin secretion.

- to arrest gonadotropin-dependent precocious puberty in children.
- to provide a ‘chemical’ castration for treatment of hormone-dependent cancers (androgen-dependent prostate cancer in men, estrogen-dependent breast cancer in women), as well as other hormone-dependent disorders (e.g. endometriosis, uterine fibroids, polycystic ovarian syndrome). One may need to administer an antiandrogen or antiestrogen at the beginning of the treatment period because the GnRH agonists initially
Gonadotropin-Releasing Hormone

induce gonadotropin release and actually stimulate gonadal steroidogenesis; it is this initial secretion of gonadotropins that may be avoided with the use of GnRH antagonists under development.

- to suppress endogenous preovulatory surges of LH in assisted fertilization techniques that employ administration of exogenous gonadotropins (see below). This obviates concern with release of endogenous hormones and allows more precise control of the timing of ovulation by the exogenously administered hormones.

Four GnRH agonists are currently available to suppress gonadotropin secretion (leuprolide acetate, histrelin acetate, nafarelin acetate and goserelin acetate). The major differences among these drugs is in their potential routes of administration (given below for each, FYI) since all are effective at inhibiting gonadotropin release. These agents are not available orally, but can be taken as sc injections or intranasal spray on a daily basis or by depot administration allowing release over ~ 1 month (either sc or im).

- **leuprolide acetate** (sc, once daily; or im, monthly)
- **histrelin acetate** (sc, once daily)
- **nafarelin acetate** (intranasally, once daily)
- **goserelin acetate** (sc injection with continuous release over 28 days)

**Side Effects**

The side effects resulting from long-term GnRH treatment are essentially those of hypogonadism and limit their use in adults to ~ six months. Side effects include:

- hot flashes; vaginal dryness and atrophy; negative calcium balance and loss of bone mass; alterations in lipid metabolism, loss of libido

**IC3. Diagnostic Uses of GnRH**

To test pituitary function in patients with gonadotropin deficiency.

Gonadotropin deficiency can reflect either a hypothalamic or a pituitary defect. If the primary defect is hypothalamic, GnRH will elicit an increase in LH release; if the defect is at the level of the pituitary, there will be no increase in LH following GnRH administration.