

Adrenal Disease and the Therapeutic Effect of Lupron

By John Hines

1. Naturally occurring steroids in the mammal

While the word "steroid" often receives negative attention due to the use of synthetic steroids by professional athletes, it has long been known that the mammalian body produces a number of its own natural steroids which are essential for normal functioning of the body. It has been useful to divide the natural steroids produced by the mammalian body into two groups:

- a. the androgens (a.k.a. the "sex steroids") — which are produced primarily by the gonads (testicles in the male animal, and ovaries in the female animal). Examples of sex steroids include estrogen, progesterone and testosterone. The androgens are important for normal sexual development and reproduction.
- b. the corticosteroids (a.k.a. the "adrenal steroids") — which are produced by the cortex (outermost layers) of the adrenal gland. Examples of adrenal steroids include cortisol and aldosterone. The adrenal steroids are important for maintaining normal metabolism and body fluid electrolyte balance. The production of corticosteroids is controlled separately from production of sex steroids.

While this neatly classifies natural steroids by their site of production and is still very useful for a basic understanding, it has been discovered that sex steroids can also be produced in small amounts by the adrenal gland. Thus, the production of sex steroids can continue even in neutered animals lacking gonads. Ordinarily, this continued production of sex steroids has little consequence, since the animals are incapable of reproducing.

However, in the case of adrenal disease in the domesticated ferret (a.k.a. hyperadrenalcorticoidism), the adrenal gland begins to produce much higher amounts of sex steroids than it would normally. This elevated level of sex steroids will lead to the very serious health problems associated with adrenal disease. It is not known for certain what causes the adrenal gland to become overactive — there may be more than one possible cause. It is known that under normal conditions the adrenal gland is controlled by the pituitary gland, as part of an overall endocrine system called the "HPA axis."

2. The HPA axis:

The adrenal glands, located above the kidneys, are under the chemical control of the pituitary gland, which is located below the base of the brain; in turn, the pituitary gland is under the direct control of an area of the brain known as the hypothalamus. Together, the hypothalamus, pituitary and adrenal glands form one of the major endocrine systems of the body, commonly called the H-P-A axis (see fig. 1).

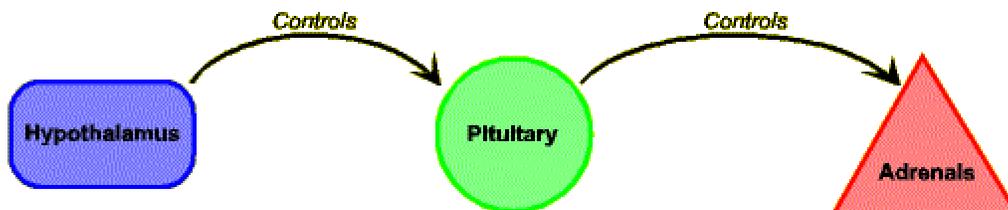


Figure 1: The Hypothalamus–Pituitary–Adrenal, or HPA Axis

In the context of sex steroid production (by either the gonads or by the adrenal glands), the hypothalamus first releases a chemical called GnRH (gonadotropin release hormone) which goes directly to the pituitary, GnRH is released by the hypothalamus in short, discrete pulses — not in a steady stream. In response to GnRH, the pituitary is itself stimulated to release its own hormones, which are called luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The LH and FSH enter the bloodstream and will travel to the gonads to stimulate production and maturation of sperm or ovum for reproductive purposes (fig. 2). They will also increase the level of sex steroids produced by the gonads.

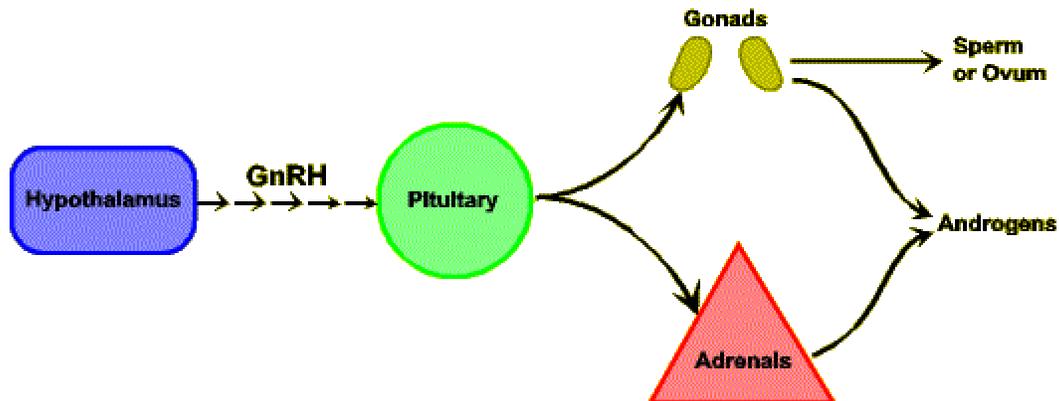


Figure 2: Normal Androgen Production via Pathways of HPA Axis

Since the adrenal glands are also capable of limited production of sex steroids, they too will respond similarly to the LH and FSH, and increase their androgen output.

3. Overproduction of sex steroids in adrenal disease:

The problem of adrenal disease in ferrets arises when a small portion of the adrenal gland called the zona reticularis begins to overproduce and release sex steroids into the body. The most direct method of correcting this problem has been removal of the affected adrenal gland(s): no more adrenal gland means no more zona reticularis, therefore no more sex steroids (assuming the ferret has also been neutered).

The downside of this approach, aside from the general risks involved with any invasive procedure, is that removal of the adrenal gland can also deprive the body of the various other hormones that are also produced by the adrenal gland. These include the other adrenal steroids (cortisol, aldosterone) and adrenalin (which is produced in the adrenal medulla, or interior). If BOTH adrenal glands need to be removed, the ability of the ferret to make these necessary hormones will be severely diminished. Often hormone replacement therapy is necessary to ensure recovery of the ferret.

As described earlier, the adrenal glands are under the control of the pituitary gland. Hormones (FSH and LH) released from the pituitary gland into the bloodstream travel to the adrenal gland and “turn on” sex steroid production and secretion. Thus, an alternative method of reducing the secretion of sex steroid from the adrenal gland would be to block the pituitary gland from producing FSH and LH (fig. 3).

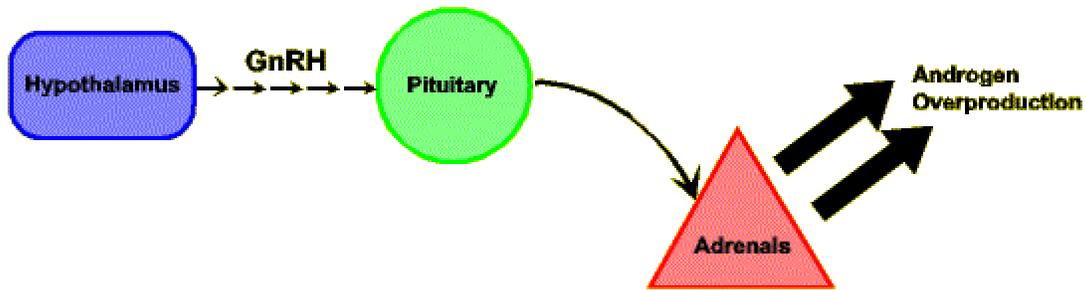


Figure 3: Adrenal Gland Overreacts to Pituitary Hormones

If these pituitary hormones were absent from the body, sex steroid production and secretion by the zona reticularis would be substantially reduced if not eliminated altogether. This approach would make the removal of the adrenal glands unnecessary and thereby spare the ferret's ability to produce the other adrenal hormones. It is by this mechanism — intervention at the level of the pituitary — that Lupron most likely can correct hyperadrenalcorticoidism.

4. How Lupron works:

As mentioned earlier, GnRH is released by the hypothalamus in a pulsatile manner to stimulate the pituitary to release FSH and LH into the bloodstream. It is necessary for normal pituitary function that the hypothalamus release GnRH in brief, discontinuous pulses rather than sustained, continuous secretion. The pituitary gland can and will rapidly lose its responsiveness to GnRH if exposed to the chemical for extended intervals of time. This phenomenon is called "desensitization."

Lupron (leuprolide acetate) is a synthetic version of GnRH. It is more stable than the natural hormone and therefore is degraded much more slowly within the body. This is the key to how Lupron works. Once injected into the bloodstream, Lupron acts at the pituitary gland just as natural GnRH does. However, since Lupron is administered at a relatively high dosage and isn't degraded easily, the sustained presence of the drug actually causes the pituitary to desensitize, and thus cease production of LH and FSH (fig. 4).

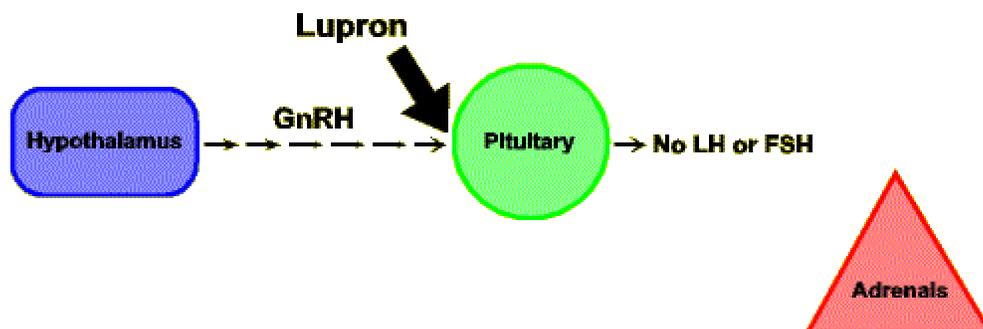


Figure 4: Desensitization of Pituitary by Lupron

Without circulating FSH and LH, the adrenal gland stops production of androgens, and thus the blood levels of androgens drop and the ferret recovers from hyperadrenalcorticoidism.

5. Limitations of Lupron Therapy:

While some ferrets with adrenal disease do well on Lupron, the scenario where a ferret may be unresponsive to Lupron may also exist. This scenario could arise if the adrenal gland has become diseased in a way such that the zona reticularis will produce androgens independent of any regulation by FSH and LH. If this should occur, the adrenal gland would probably continue to hyper-secrete androgens even after Lupron therapy has reduced levels of FSH and LH. However, since some ferrets do respond well to Lupron, it is often worth trying if the ferret owner is uncomfortable with the idea of surgery as a first remedy.

Also, Lupron therapy is a life-long protocol: the ferret will require regular doses of Lupron to keep the malfunctioning adrenal gland under control. In the long run, this can be more expensive than surgery, which is presumably a one-time procedure.

References

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John Hines earned his Ph.D. in pharmacology at the University of Pennsylvania and currently works in the Lab of Pharmacology at its School of Veterinary Medicine. Akasha and Nikita, his two beloved ferrets, have sadly gone before him to the Rainbow Bridge, and are hopefully patiently awaiting his arrival there. Nikita and Akasha received excellent veterinary care at the Animal and Bird Health Care Center in Cherry Hill, NJ.

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