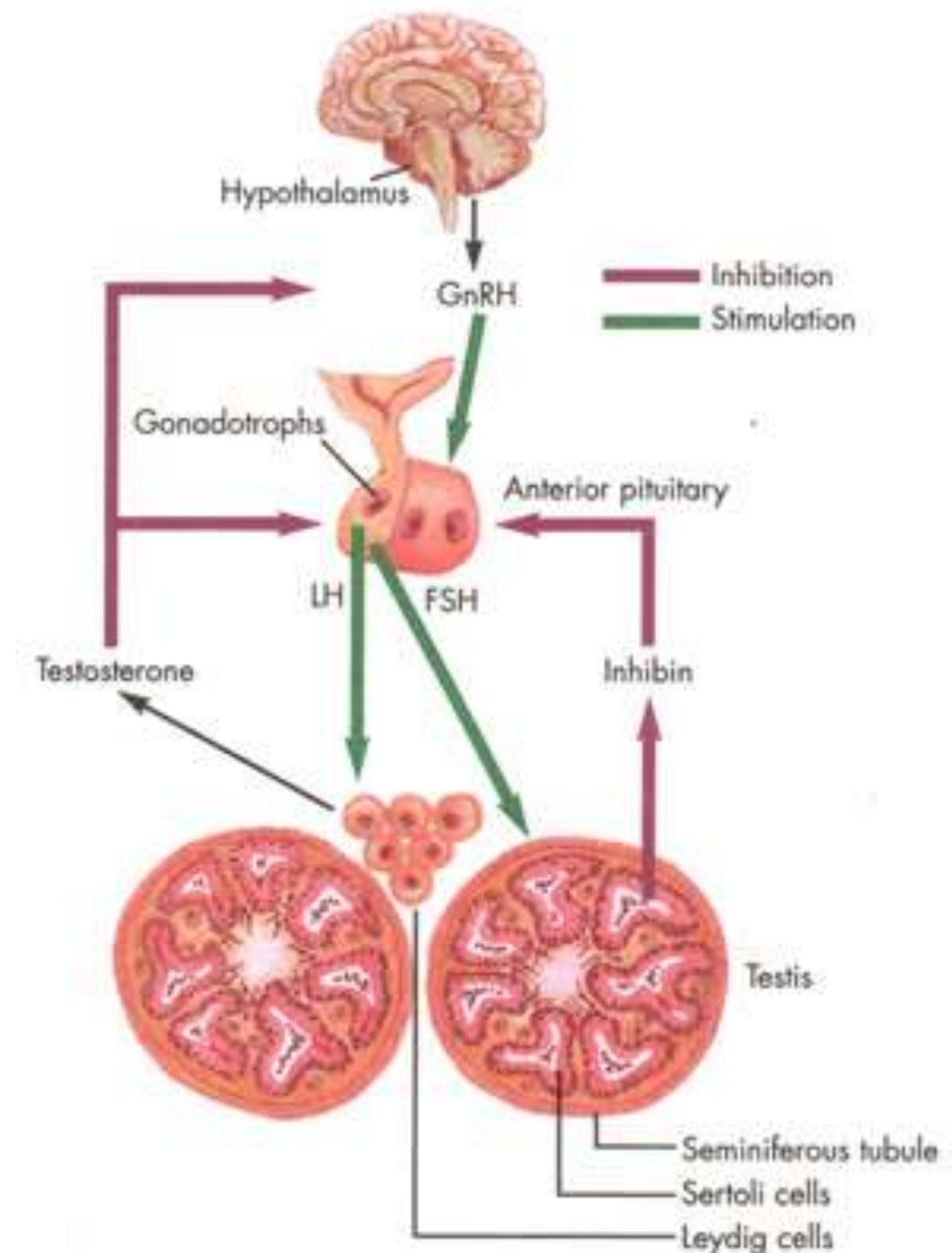


GnRH Agonists Alter Body Composition After Long Term Exposure

Grace Shearrer, (Brian S. Edwards, Arik W. Smith and Donal C. Skinner)

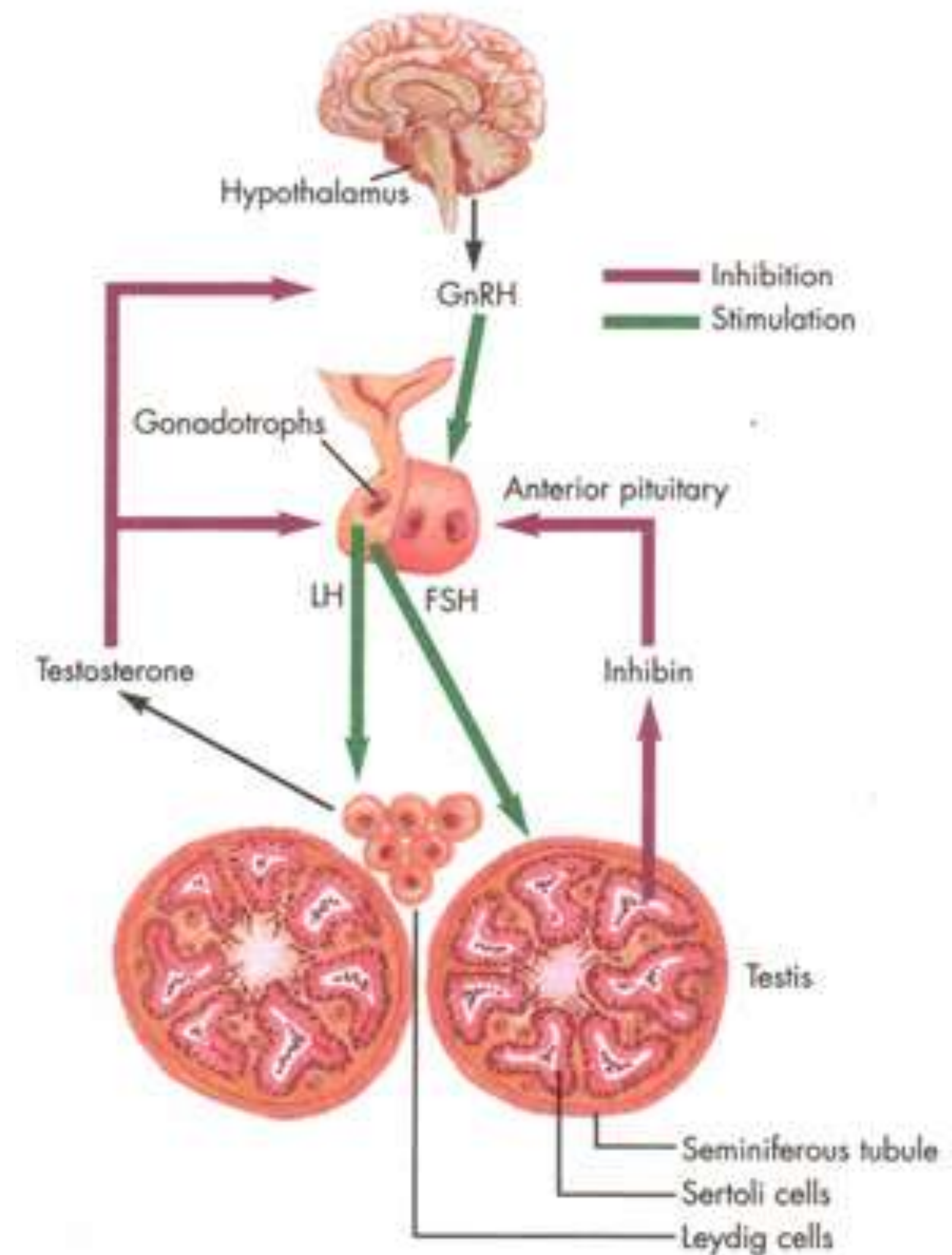
The Reproductive Axis

- The reproductive axis in mammals has three key players: the **hypothalamus**, **pituitary**, and **reproductive organs**.
- The hypothalamus is a portion of the brain which releases **neurohormones**.
 - One such neurohormone is **Gonadotropin-releasing hormone (GnRH)**.
 - GnRH is released from the hypothalamus and stimulates the pituitary gland.
- The **pituitary gland** sits beneath the brain.
 - The GnRH acts on the pituitary gland signaling for the **release of two hormones**:
 - **Luteinizing Hormone (LH)**
 - **Follicular Stimulating Hormone (FHS)**



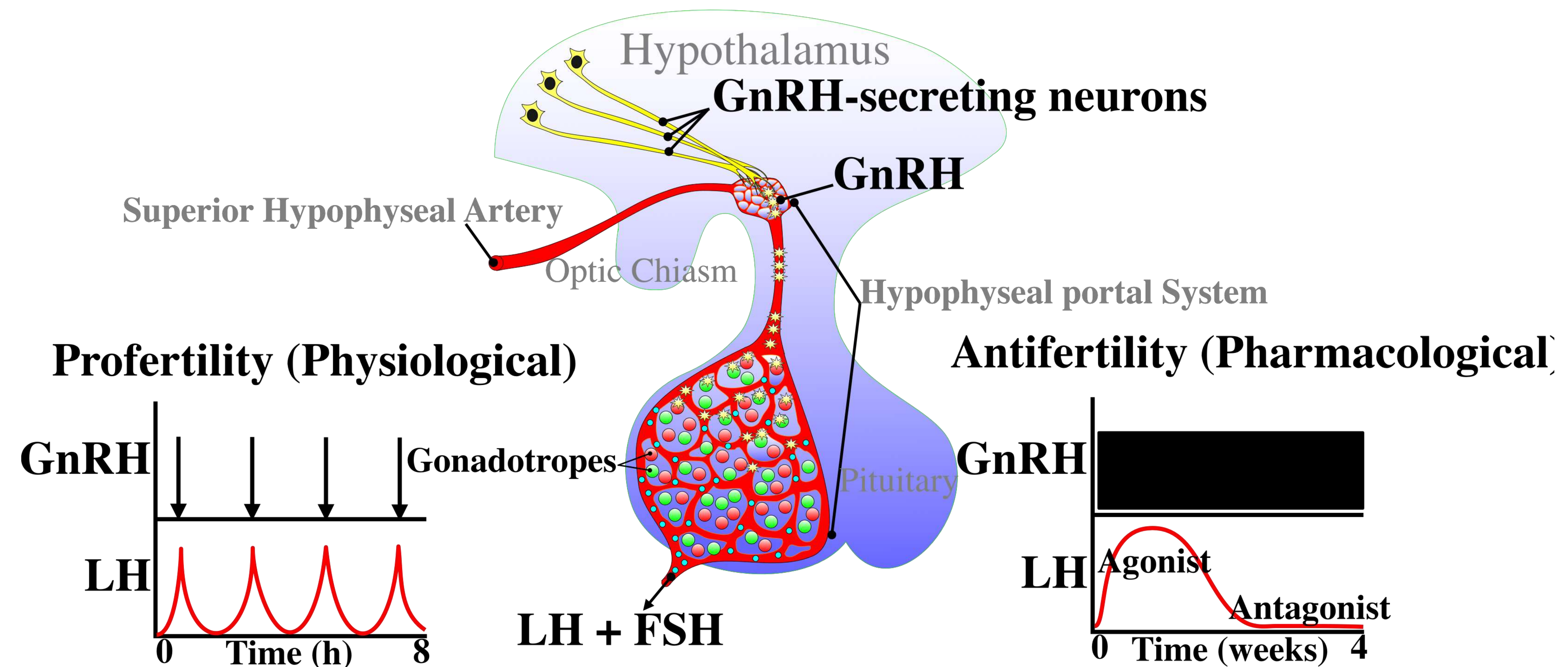
The Reproductive Axis

- LH and FSH further act on the Leydig cells and Sertoli cells of the testes in male mammals to promote sexual maturation.
 - Further stimulates the release of androgens, such as **testosterone**.
- In females, LH and FSH regulate the onset and continuation of menses.
- The reproductive axis is self regulating through a **negative feedback mechanism**.
 - **High levels** of any of the component hormones act to **shut down the axis**.
 - This is accomplished through an intricate interaction between various receptors in the hypothalamus and pituitary gland.



Using a Negative Feedback Mechanism for Good

- A GnRH agonist mimics constant exposure to high levels of GnRH from the hypothalamus.
- The high levels of GnRH suppress the reproductive axis through desensitization.
- GnRH agonists have proven useful in the treatment of a bevy of disorders, including:
 - Endometriosis
 - Uterine fibroids
 - Polycystic ovarian syndrome
 - **Prostate Cancer**

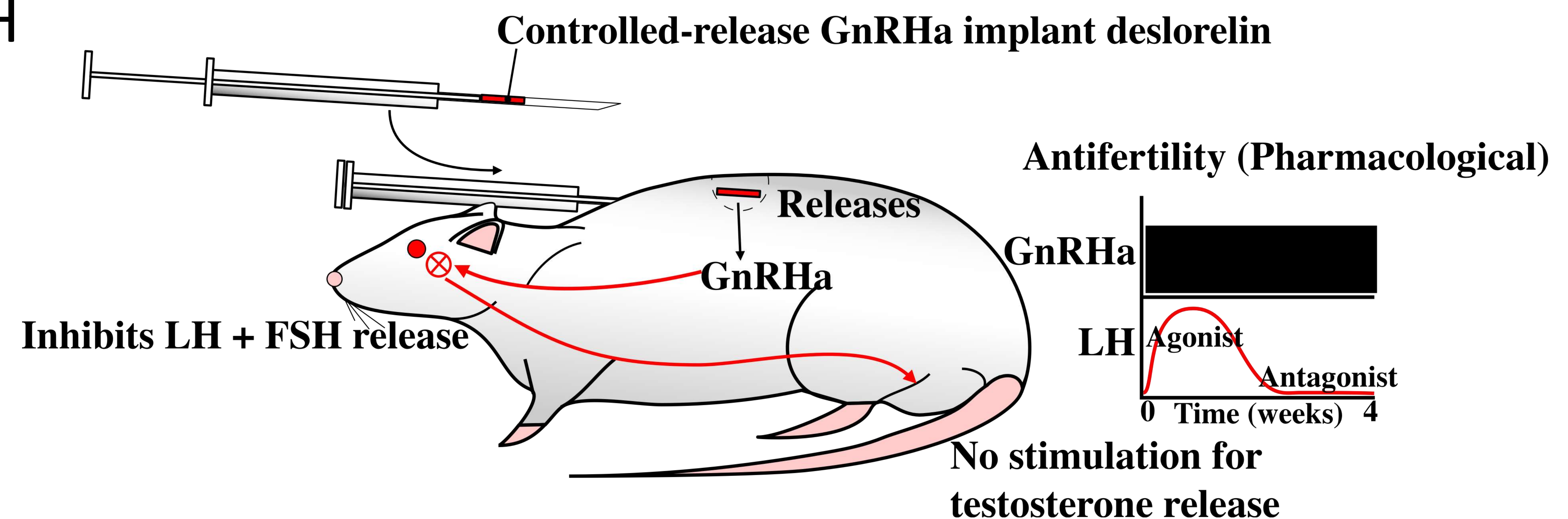


GnRH Agonists and Prostate Cancer: A Love Hate Relationship

- 600,000 men received GnRH agonist therapy in 2007 in the US alone.
- However, GnRH agonists are not without side effects.
- In humans, GnRH agonist therapy is associated with **increased subcutaneous adiposity**, with a **decrease in lean mass and muscle**.
- Men receiving a GnRH agonists often experience:
 - Hot flashes
 - Weight gain
 - Increase risk of **diabetes**
 - Increase risk of **osteoporotic fracture**
- Most alarming is the marked **increase in risk of cardiovascular disease (CVD)**.
 - In October of 2010 prompted the FDA to issue a warning concerning GnRH agonists and CVD.

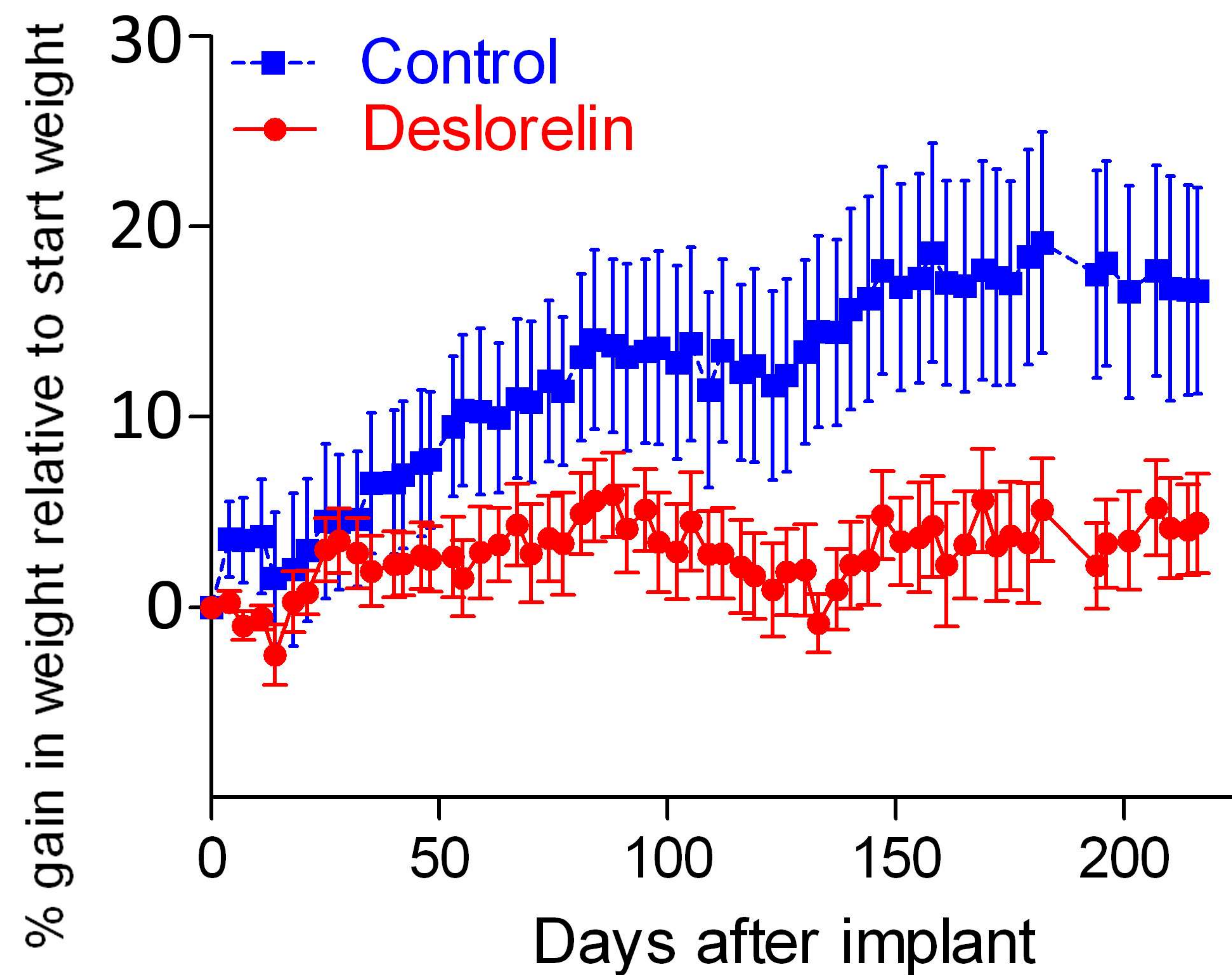
Materials and Methods

- Adult male 137 day old Sprague-Dawley rats were treated subcutaneously for 6 weeks or 8 months with a sham implant or a slow-release low (1.1mg) or high (14.1mg) dose deslorelin implant (GnRH agonist; Suprelorin[®]; Peptech Animal Health).
- Implants were removed at the end of treatment.
- To determine whether effects were testosterone dependent, a subset of the 6 week rats were treated with a testosterone implant.
- An additional subset was castrated.

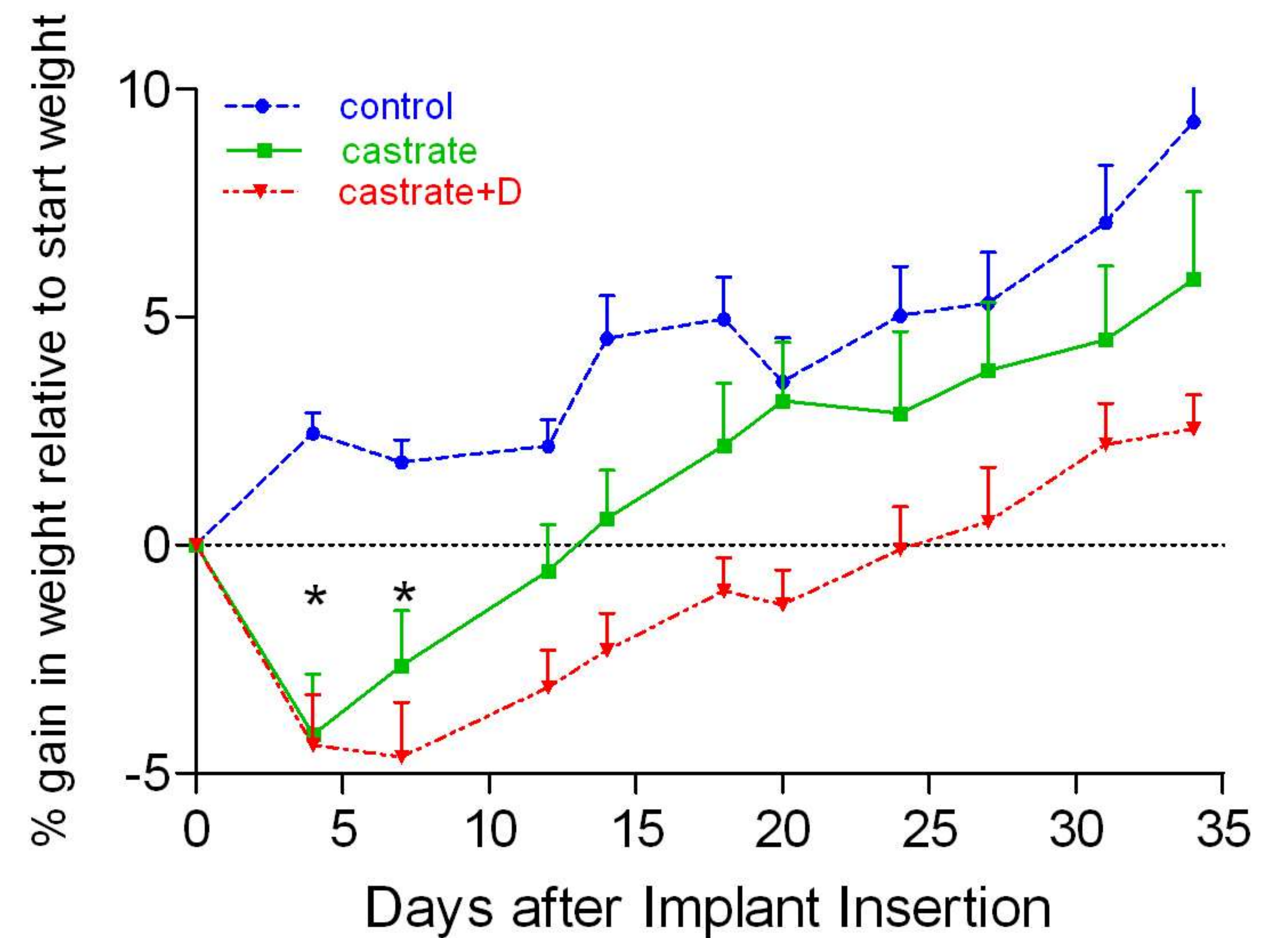


Results

8 months 1.1mg Deslorelin

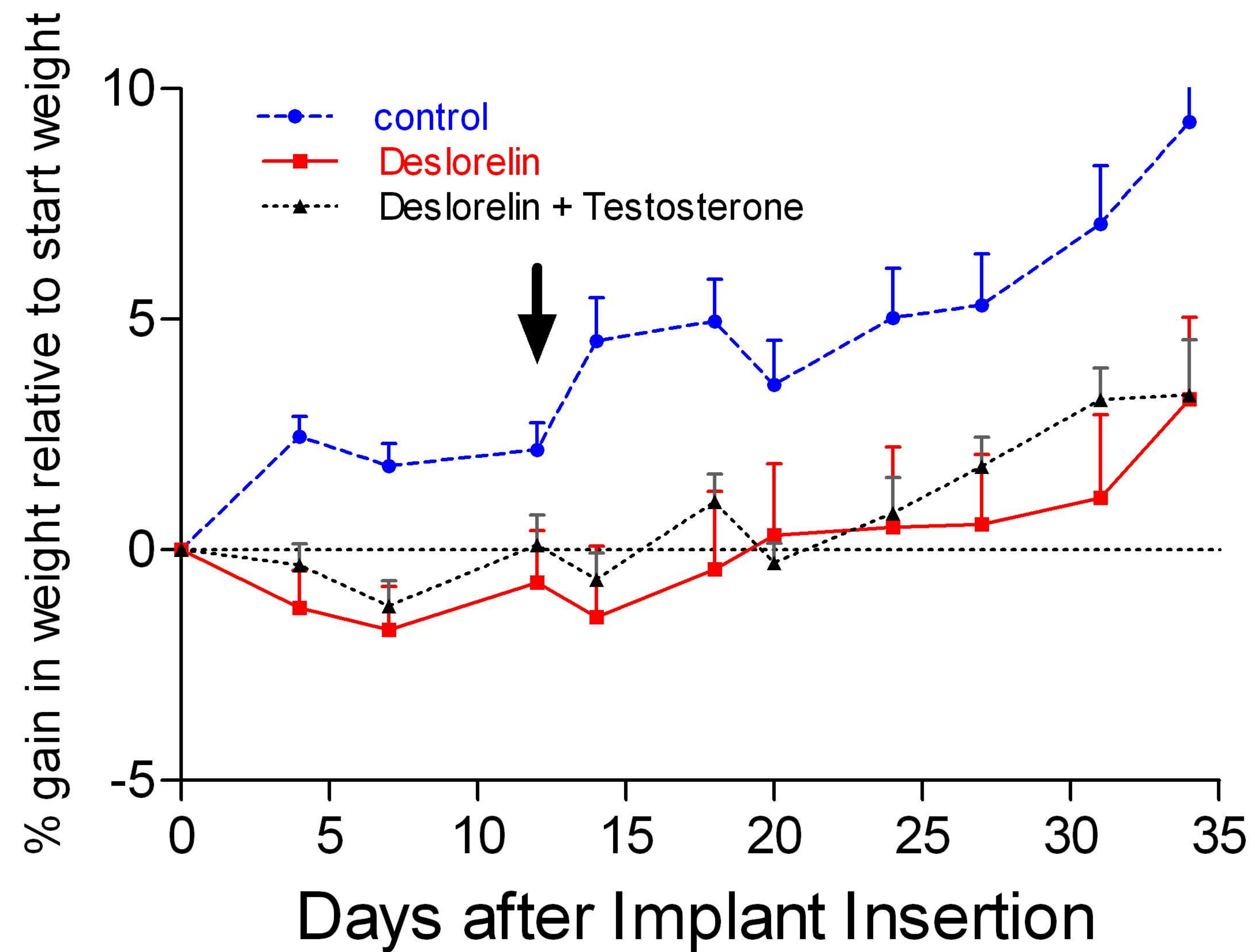


Deslorelin & Castration on BW

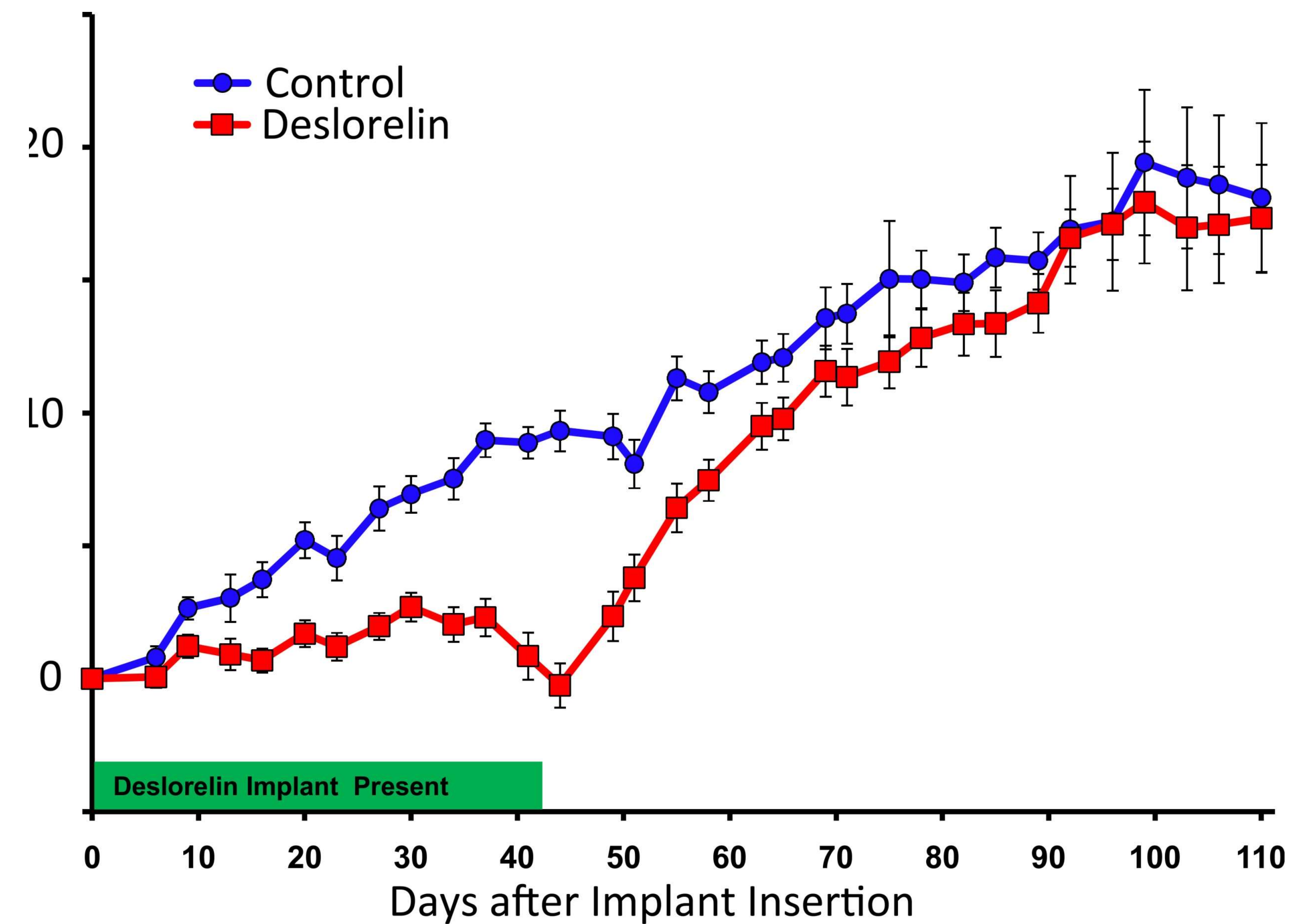


Results

1.1mg Deslorelin & Testosterone on BW



Recovery from 6 weeks 1.1mg Deslorelin



What does it mean Basil?

- The data shows an apparent arrest and decrease in weight gain in male rats.
- The reduced weight appears to be independent of testosterone.
- Despite an increased duration of exposure to a high dose enhances testicular atrophy (see picture), body weight is not further compromised.
- In humans, GnRH agonists are well implicated in the **decrease of lean body mass, decrease in muscle size and increase in subcutaneous fat.**

Testes



What does it mean Basil?

- The alteration of lean versus fatty mass has significant metabolic implications.
- **Increased subcutaneous adiposity** is a well know risk factor for both **diabetes and CVD**.
- Decreased muscle size and lean body mass contribute to **sarcolema**.
 - Other studies also suggest that GnRH agonists contribute to **decrease bone mass**.
 - The combination of sarcolema and decrease bone density could explain the **high fracture risk**.

Testes



Where Do We Go From Here?

- The interplay between GnRH and their ability to alter metabolic profile over an extended period is largely unstudied.
- Further research (summer, 2011) will explore the effect of GnRH agonists on lean muscle and fat deposition, as well as the effects on bone mineral content.
- **Lipid panels** will be used to explore variations in triglycerides and cholesterol levels in male rats.
 - Triglyceride composition in the body are key determinants in CVD and diabetes risk.
- **Insulin and glucose measurements** will be assessed to further investigate possible diabetes risk.
 - Diabetes is an independent risk factor for CVD.
- **Enzyme-linked immunosorbent assay (ELISA)** will be used to perform hormone analysis.
 - Increased hormone levels could implicate GnRH working in previously unknown endocrine pathways such as:
 - Leptin
 - Insulin

Where Do We Go From Here?

- Dual-energy X-ray absorptiometry (DEXA) scans will also be preformed.
 - DEXA will allow us to track changes in bone metabolism in the same animals over an extended period of time.
 - DEXA also will allow us to see changes in adiposity in the animals' bodies.
- To further test bone mineral content, EDTA titrations will be preformed to determine calcium and magnesium concentrations.
- Atomic absorption spectroscopy will also be used to analyze phosphorous concentrations.



Acknowledgements

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- A special thank you to my primary investigator Donal Skinner and his graduate students Brian Edwards and Arik Smith