



# Prostate Regulation: Modeling Endogenous Androgens and Exogenous Antiandrogens

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research development

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## Science Question

Antiandrogens perturb hormonal regulation of the male endocrine system. Prostate function is a particularly sensitive response for androgen function. The dose-response characteristics of the system are not well characterized.

Antiandrogens include both environmental and pharmaceutical compounds. Fungicides, such as vinclozolin and procimidon, and pharmaceutical agents, such as flutamide and bicalutamide are androgen receptor antagonists. Pharmaceutical inhibitors of 5 $\alpha$ -reductase conversion of testosterone to dihydrotestosterone (DHT), include finasteride. Castration is a commonly used surgical hormonal perturbation.

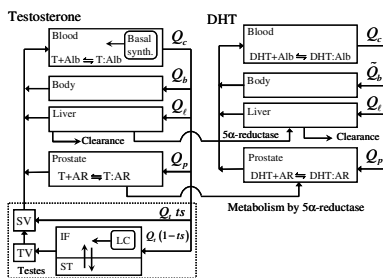
## Research Goals

Develop a model for the androgenic regulation of prostate function in intact and castrate rats.

Incorporate antiandrogen pharmacokinetics and perturbations of prostate function.

Extend model with pubertal transition to evaluate dose-response in pubertal assays.

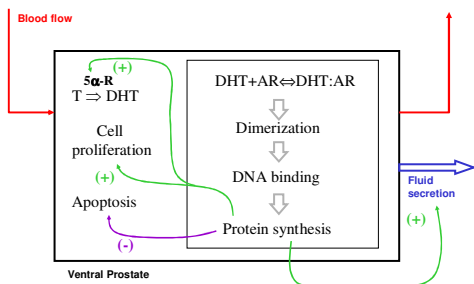
## Pharmacokinetics:



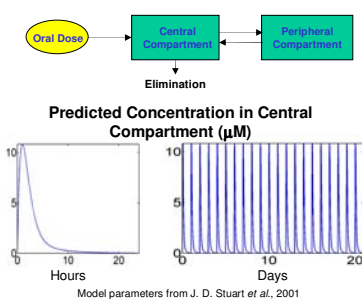
In addition to the pharmacokinetic models above for testosterone and DHT, the model incorporates a compartmental model for luteinizing hormone (LH). There is an empirical description of the feedback loop between LH and testosterone.

## Pharmacodynamics:

### Prostate: Gene to Tissue Response



### Two-Compartment PK model for Finasteride

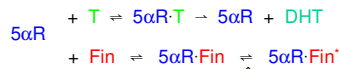


### Modeling Different Enzyme Inhibition Mechanisms

#### Competitive Inhibition of Hepatic 5 $\alpha$ -Reductase: T $\rightarrow$ DHT

$$\frac{V_{MAX} \cdot C^T_{prostate}}{K_M \left( 1 + \frac{C_{central}}{K_I} \right) + C^T_{prostate}}$$

#### Time-Dependent Inhibition of Prostatic 5 $\alpha$ -Reductase: T $\rightarrow$ DHT



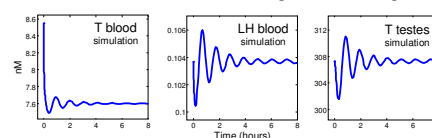
#### 5 $\alpha$ -reductase isoforms

**Type 1:** Located throughout the body, high in liver, low in prostate. Finasteride competes competitively with T for 5 $\alpha$ -reductase type 1. Reversible enzyme inhibition.

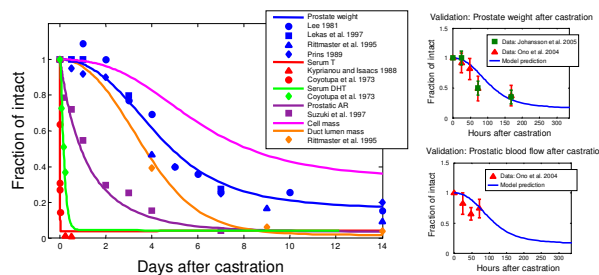
**Type 2:** High concentrations in prostate, low in most other tissues. Finasteride exhibits time-dependent inhibition of 5 $\alpha$ -reductase type 2. Very slow off rate (~30 d). Virtually irreversible enzyme inhibition.

## Model Simulations:

### Predicted Serum Hormone Concentrations after Simulated 0.02 nmol iv Dose of T Demonstrating Feedback Regulation

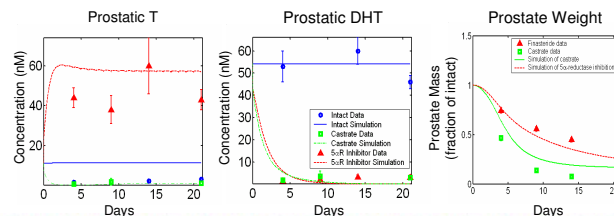


### Predicted Prostate Regressions Following Castration: Model Calibration and Validation



**Data:** Rittmaster et al., 1995 **Experimental Conditions:** 40 mg/kg Finasteride daily for 21 d. **Reported:** Hormone concentrations and prostate mass for intact, finasteride treated and castrated rats at days 4, 9, 14, 21

### Finasteride Challenge



## Results/Conclusions

The time course of prostate responses to androgen deprivation by castration or finasteride treatment is successfully reproduced by this combined biologically based pharmacokinetic and pharmacodynamic model. The model predicted data on prostate weight and blood flow that were not used in model parameter estimation (i.e., calibration).

## Impact and Outcomes

The model demonstrates the potential for using biologically based models to describe underlying biology and its perturbation by environmental or pharmaceutical compounds. Further developments are required to simulate the literature on androgen supplementation via silastic implants to calibrate the dose-response aspects of the model. That will result in a predictive model for the adult that could then be extended to describe the hormonal changes associated with puberty, which would be useful for interpretation of pubertal assay results.

## Future Directions

1. Intact and castrate rat modeling paper accepted in American Journal of Physiology: Endocrinology and Metabolism. Complete paper on finasteride modeling.
2. Model androgen supplementation and prostate regrowth to calibrate androgen dose-response.
3. Model androgen receptor antagonist activity in adult rat.
4. Evaluate linking model to high content data, such as prostatic gene array data for intact, castrate, and antiandrogen-treated rats.
5. Extend model to pubertal hormonal changes and dose-response in pubertal assays.

## References

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Long Term Goal III



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