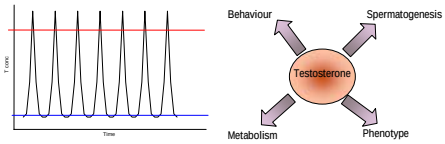
Timing feedback-inhibition of the male reproductive hormone axis

Ritu Malik,[1] Shailesh Tondwal,[2] K.S. Venkatesh,[2] Gopal Gupta,[1] Amit Misra.[1]
Pharmaceutics Division, Central Drug Research Institute, Lucknow, 226001, India [1]
Department of Electrical Engineering, Indian Institute of Technology, Kanpur-208016, India[2]

INTRODUCTION

Neurosecretion of gonadotropin releasing hormone (GnRH) is episodic (one pulse every 90-100 min) which stimulates LH
LH in turn stimulates episodic release of testosterone (T) in the testes (Turek et al, 1994).



High intra-testicular T is a requisite for spermatogenesis in the testis. Hence episodic secretion of all the three hormones is essential for fertility.
Clinical trials have demonstrated the contraceptive potential of feedback-inhibition of endogenous T production (Grimes et al, 2004).

Supplementation of endogenous T is currently incapable of restoring fertility. (exogenous T delivery-*CONTINUOUS*)
Intensive sampling of peripheral blood, at intervals of 2-10 minutes (*Heroic!*)
Established computational models of the hypothalamus-pituitary-gonad- (Veldhuis et al, 1998)
Test the hypothesis- inhibition of GnRH and/or LH secretion by T (*pulsatile?*)

A long-standing evidence shows that such depriviation, results in atrophy of the pituitary (Drewett et al, 1993).

This report addresses the pulsatile approach to feedback-inhibition and tests the hypothesis of episodic interference in HPT axis in silico and in vivo. The model addresses the effect of chronic GnRH deprivation on the viability of pituitary gonadotrophes which has been illustrated to have in vivo correlation.

OBJECTIVES

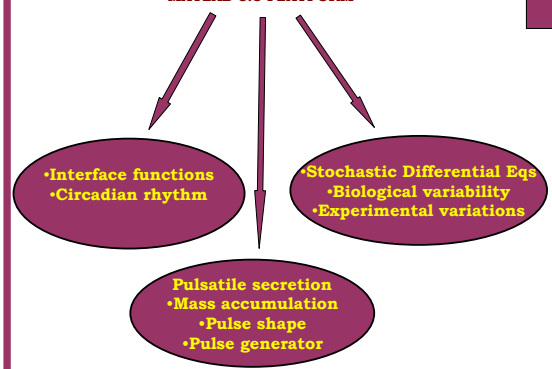
- To implement a computational model of male reproductive hormone secretion and modify it further for suggesting a parsimonious, stand-alone male contraceptive regimen using T alone.
- To test certain hypotheses about male contraception using exogenous T alone.
- To test the contraceptive efficacy of the prepared formulations delivering a pulsatile profile.

METHODS

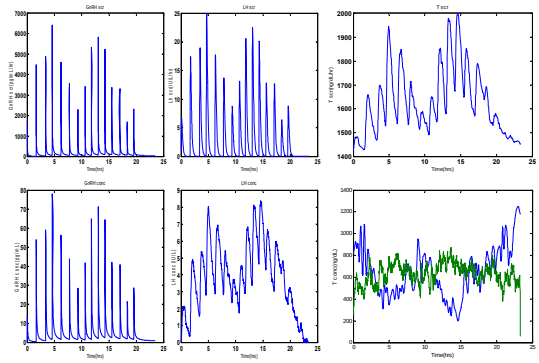
- The model of the HPT axis (Veldhuis et al, 1998) was implemented using MATLAB 6.5 platform in collaboration with IIT, Kanpur. Basal and pulsatile secretion rates of GnRH, LH and T were rebuilt from observed plasma hormone concentration time series.
- Data depicting the periodicity in the HPT axis over 4 months was generated to test the efficacy of reported and fabricated T delivery systems in silico.
- Simulations were done for sustained and pulsatile delivery of T alone as well as marketed formulations delivering T using the above model.
- Formulation of a 'viability function' describing the degeneration and repopulation of LH-producing cells in the pituitary and evaluation of gonadotrophe viability in rats after prolonged administration of pulsatile external T .
- The effects of the regimen using fabricated systems on spermatogenic status and reproductive capacity have been assessed by studying testicular histology.

COMPUTATIONAL MODEL

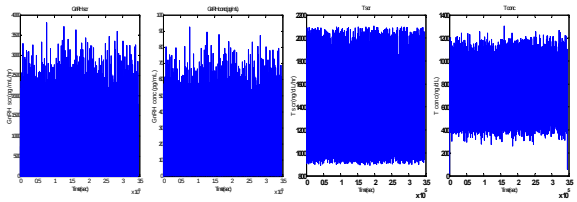
MATLAB 6.5 PLATFORM



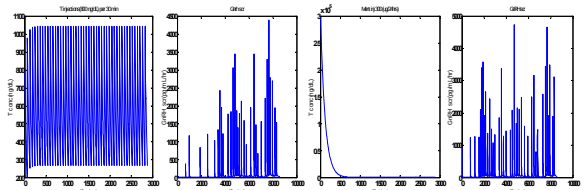
HORMONE SECRETIONS AND CONCENTRATIONS/DAY



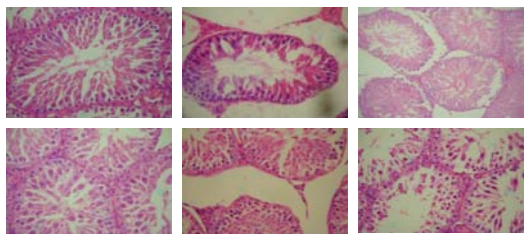
HORMONE SECRETIONS AND CONCENTRATIONS OVER 4 MONTHS



SUSTAINED AND PULSATILE T DELIVERY SIMULATIONS



EFFICACY OF PULSATILE T DELIVERY SYSTEMS: SPERMATOGENIC STATUS



DISCUSSION

- The predicted profiles maintain pulsatility and a circadian rhythm, showing the dynamic nature of the model. Intervention of the HPT axis by transdermal patches delivering T, led to suppression of all three hormone concentrations and secretions with loss of pulsatility in them. The simulated construct for 4 months was dynamic in itself with proper suppression shown on application of external T due to its feedback on succeeding processes.
- Pulsatile administration of T injections amounting to a total of only 38.4 µg of T a day gave better suppression of GnRH secretion in comparison to a single daily dose of 300 µg of MENT (T analog).
- Pulsatile administration of a smaller dose of T suppresses the pulse generator to a greater extent than pulsatile administration of a larger dose of MENT, probably due to more rapid changes in instantaneous T concentrations.
- The secretion and concentration of LH and T decrease during 4-month T regimen and pulsatile, baseline T is maintained throughout this period indicating suitability of the regimen for contraception.
- Pulsatile T acts at the step of the conversion of round spermatids between stages VII and VIII which is not restored even after 30 days of withdrawal of T treatment.
- The extent of apoptosis of LH gonadotropes in rats on day 136 (after 4 weeks of recovery) correlates with suppression of LH secretion as proposed by model after T-treatment.

CONCLUSIONS

- The dynamic nature of the model includes the ability to self correct in anticipation of expected T concentration in the past. This also indicates the need for contraceptive T regimens to be variable rather than repetitive, in addition to being pulsatile.
- Incorporation of the vitality function in the model allows the prediction of a "holiday period" in the contraceptive regimen, during which exogenous T would not be needed to protect from conception.
- Incremented disruption of spermatogenesis is observed in T treated animals as compared to sham-treated animals.

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MODEL PREDICTED GnRH SECRETION IN PRESENCE OF VITALITY FUNCTION AND VIABILITY OF LH GONADOTROPES