A Model for the Control of Testosterone Secretion

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We produce here a model to explain the control of testosterone secretion. In this model the hypothalamic secretion of the hormone LHRH (luteinizing hormone releasing hormone) is controlled by a combination of local testosterone concentration and of the local concentration of the pituitary hormone LH (luteinizing hormone). Since LHRH stimulates the release of LH, and LH in turn stimulates the release of testosterone, the three hormones constitute a three-component “feedback” network. We show how this model is able to account for the pulsatility of the release of these three hormones. Furthermore, the model is consistent with results obtained from a wide range of experimental manipulations of the system. For example, it accounts for the changes observed in hormone release patterns after castration. In particular, it follows that no “neural clock”, or “neural pulse-generator”, is required to force the system into pulsatile behaviour.

Introduction

It is now recognized that blood testosterone levels fluctuate over the short term (2-3 h in humans). The secretion of testosterone from the testis is stimulated by the pituitary hormone LH (luteinizing hormone); the production of LH is stimulated, in turn, by the hypothalamic hormone LHRH (luteinizing hormone releasing hormone). The fluctuations in testosterone levels can then be traced back to the pulsatile release of LHRH (Lincoln, 1979).

Several models have been put forward to try to account for the pulsatile release of these three hormones. These models fall into two classes. Those in the first class assume the existence of a “neural clock”, a pulse-generator which forces the hypothalamic secretion of LHRH, and thus drives the entire system. Models of the second kind assume no external pulse input: in these models the pulsatility is a consequence of the interactions between the three components of the system—“feedback oscillations”.

That testosterone has a controlling effect on the output of LHRH from the hypothalamus is irrefutable, as data from castrates show (Ellis & Desjardins, 1984; Gay & Sheth, 1972; Södersten et al., 1983; Steiner et al., 1982). Thus, advocates of the “neural clock” models must also assume that although “the LHRH pulse

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generator... runs continuously... [it] is primarily controlled through inhibition by gonadal steroids" (Lincoln et al., 1985). These models do not describe the inhibitory mechanism, and are therefore not really models at all.

Existing models of the second class (in which there is no neural clock) envisage the suppression of LHRH production solely by high testosterone levels (for example Smith, 1980). These models are also inadequate, for they cannot explain the pulsatility of LH release observed in castrates (Ellis & Desjardins, 1984; Gay & Sheth, 1972; Plant, 1982; Södersten et al., 1983; Steiner et al., 1982).

In this paper we present a new model. This model does not resort to using a neural clock. By allowing both LH and testosterone to regulate the output of the hypothalamus, it accounts for all the phenomena described above.

Although the model we describe here has been formulated for the LHRH/LH/testosterone system, the approach is likely to be much more widely applicable.

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**A Description of the Model**

The model we propose has the following features (see Fig. 1).

(i) There are three active components—the hypothalamus, the (anterior) pituitary, and the testis.

(ii) The rate of LH release from the pituitary depends linearly (or nearly so) on the local concentration of LHRH. Likewise, the rate of testosterone synthesis by the testis depends linearly on the local LH concentration.

(iii) The synthesis of testosterone takes a fixed, finite time. Thus there is a (fixed) delay between the stimulation of the testis by LH and the eventual release of testosterone into the bloodstream.

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**Fig. 1.** Summary of the model schema proposed in the test for the LHRH/LH/testosterone system. The three components of the system are the hypothalamus (H), the pituitary (P), and the testis (T). The hypothalamus secretes LHRH (double line), which controls the pituitary release of LH (single line). In turn, LH controls the secretion of testosterone (dashed line) by the testis. The novel element of our model is a hypothetical control unit (+) which combines the concentrations of LH and testosterone. The output of this unit is a control signal (dot-and-dash line) to the hypothalamus, which controls LHRH secretion. The nature of this control unit is unclear. It might be intrahypothalamic or neural; it might be biochemical or biophysical.
There are also transport delays (of fixed length) owing to the time taken for the hormones to travel from source to destination across the body.

(iv) The hypothalamus has an "on" state and an "off" state. In the "on" state, it secretes LHRH at a constant rate; in the "off" state, it does not secrete. It is switched on by a combination of a low local LH level and a low local testosterone level.

(v) Each of the hormones is cleared from the bloodstream at a rate proportional to its concentration—that is, according to first-order kinetics. Thus the concentration of each hormone is affected by the complementary processes of synthesis and clearance.

Each of these points requires comment.

(i) By "the hypothalamus" we mean the neurones in the medio-basal hypothalamus which secrete LHRH (Silverman et al., 1982). Similarly, "the pituitary" refers to the gonadotrophs, those cells which secrete LH; and "the testis" is taken to be the (sole peripheral) site of testosterone production.

In fact, of course, the adrenal glands also secrete some testosterone (Parker & Odell, 1980). For the purposes of the model, the adrenal contribution is counted as part of the testis production.

(ii) The assumption of linearity in the pituitary and testis response is clearly a simplification. It is known that at high stimulant concentrations the outputs level off to a maximum rate of production, and that therefore the response is not strictly linear (Mendelson et al., 1975; O'Connor et al., 1980). Nevertheless, our assumption of linearity is a good approximation under physiological conditions.

The dependence of testosterone production rates on intratesticular ("paracrine") factors is not well understood (Sharpe, 1986). (Such factors might operate within our system by modifying, in some way, the sensitivity of the testis to blood LH levels.)

Furthermore, in females the output of the pituitary depends on the recent history of exposure to LHRH (the phenomenon of "priming"; see Fink et al., 1976), and it is possible that a similar effect is present in males. The model we propose might be adapted when the mechanisms of these effects are understood. At the present time, it seems preferable to neglect these effects.

(iii) Kinetic analysis of stimulated Leydig (testicular) cells by Mendelson et al. (1975) shows that 20-25 min elapses between their stimulation and any significant production of testosterone, and that the equilibrium production rate is reached soon thereafter. The data also show that the production delay is independent of stimulant concentration.

Transport delays are unlikely to be constant. There is more likely to be a spread of arrival times, dependent on which path is taken. Moreover, physiological state is likely to affect the timing, for example by vasodilation and vasoconstriction. However, neither of these effects is likely to introduce any substantial changes in the predictions of our model.

(iv) That the hypothalamus is active episodically has been established both electrophysiologically and from the collection of blood from the hypothalamo-hypophyseal portal system (Carmel et al., 1976; Dluzen & Ramirez, 1983; Wilson et al., 1984). The effect of testosterone on the hypothalamus is clear from observations
of castrates (Dluzen & Ramirez, 1983; Ellis & Desjardins, 1984; Gay & Sheth, 1972; Södersten et al., 1983; Steiner et al., 1982). There are few data on the effects of LH on the hypothalamus (Motta et al., 1969; Gay, 1974), but they are not inconsistent with our model.

Quite how the LH level and the testosterone level in the vicinity of the hypothalamus would best be combined to regulate LHRH release is open to speculation. In the model we present here, we assume a linear combination for the sake of simplicity. Other methods of combining the two lead to different predictions. A multiplicative combination, for instance, is one alternative: in this case it is the product of the concentrations that controls LHRH output. Data from castrates argue against this, however, for in the absence of testosterone the hypothalamus would always be switched on.

(v) The importance of the various mechanisms for the clearance of hormones from the bloodstream is not clear, but for the purposes of the model is irrelevant. Among the processes responsible for this clearance are excretory mechanisms, catabolism in the liver, and (for LHRH and LH) the effect of peptidases.

Thus, we envisage the following sequence of events.

1. LHRH is released by the hypothalamus.
2. LHRH reaches the pituitary, and stimulates the release of LH. As the LH level rises within the hypothalamus, the release of LHRH is switched off. This in turn switches off the production of LH. As a result, both LHRH and LH are secreted in pulses.
3. LH reaches the testis, and stimulates steroid synthesis. Some time later, testosterone levels begin to rise.
4. The concentration of LH decays, and following it the rate of testosterone production declines. When the concentrations of both hormones fall below a certain level, the hypothalamus is switched on again, and the cycle is repeated.

Formally, the model has three variables:

\[ R(t) \] — the concentration of LHRH at the hypothalamus at time \( t \).
\[ L(t) \] — the concentration of LH at the pituitary at time \( t \).
\[ T(t) \] — the bloodstream concentration of testosterone in the vicinity of the testis at time \( t \).

The following parameters are used:

\[ r_R, r_L, r_T \] — response rates for the production of (respectively) LHRH, LH, and testosterone.
\[ d_R, d_L, d_T \] — decay rates of the three hormones in the bloodstream.
\[ \tau_{H-P}, \tau_{P-T}, \tau_{T-H}, \tau_{P-H} \] — time taken for hormones to be transported between the hypothalamus (\( H \)), the pituitary (\( P \)), and the testis (\( T \)).
\[ \tau_0 \] — the interval between testis stimulation and testosterone release.
\[ \hat{L}, \hat{T} \] — concentration parameters related to the switching of the hypothalamus by LH and testosterone (see eqn (1) below)
The equations of control are the following:

\[ \dot{R}(t) = -d_R R(t) + r_R H(2 - L(t - \tau_{p-H})/\hat{L} - T(t - \tau_{T-H})/\hat{T}) \]  
\[ \dot{L}(t) = -d_L L(t) + r_L R(t - \tau_{H-p}) \]  
\[ \dot{T}(t) = -d_T T(t) + r_T L(t - \tau_{p-T} - \tau_0) \]  

where \( H(x) \) is the Heaviside step function:

\[ H(x) = \begin{cases} 
0 & \text{if } x < 0 \\
\frac{1}{2} & \text{if } x = 0 \\
1 & \text{if } x > 0.
\end{cases} \]

The model defined by these equations was simulated numerically on a microcomputer. The parameters were given the following values:

- \( r_R = 0.1 \text{ ng/ml/min} \)
- \( r_L = 5 \text{ min}^{-1} \)
- \( r_T = 0.01 \text{ min}^{-1} \)
- \( d_R = 0.10 \text{ min}^{-1} \)
- \( d_L = 0.015 \text{ min}^{-1} \)
- \( d_T = 0.023 \text{ min}^{-1} \)
- \( \tau_{H-p} = 3 \text{ min} \)
- \( \tau_{p-T} = 5 \text{ min} \)
- \( \tau_{T-H} = 5 \text{ min} \)
- \( \tau_0 = 25 \text{ min} \)
- \( L = 30 \text{ ng/ml} \)
- \( \hat{T} = 8 \text{ ng/ml} \)

These values were chosen partly to be "physiologically reasonable", partly to fit existing (human) data. The figure for \( \tau_0 \) was based on the data of Mendelson et al. (1975); the values of \( d_R, d_L, \) and \( d_T \) were taken from Pimstone et al. (1977), Martin (1985), and Yen & Jaffe (1978).

Figure 2 shows the limit-cycle running of this model, after transients caused by initial conditions have died away. This may be compared with data obtained from normal males (Nankin & Troen, 1971; Santen & Bardin, 1973; Winters & Troen, 1983).

Discussion

The model here presented is in substantial agreement with experimental data from normal adult males. In addition, it accounts well for the physiological changes following castration (in rats and monkeys), hormone infusion, and hormone suppression by LHRH antagonists.

After castration, there is an elevation of the baseline level of LH in the bloodstream, coupled with a substantial increase in pulse frequency. This observation invalidates simple feedback models such as the one proposed by Smith (1980), in which testosterone alone controls the production of LHRH, for in this model castration effectively opens the feedback loop and renders the system non-pulsatile. In our "two-loop" model, however, the second loop—the "short loop" between the hypothalamus and the pituitary—is still intact in the castrate. Although experimental data in humans are understandably absent, LH (and testosterone) measurements on castrated rats show remarkable similarity to the prediction of the model (see...
Fig. 2. Results of a microcomputer simulation of the LHRH/LH/testosterone system according to the mathematical model described in the text. The plot portrays the variation of the blood levels of LHRH (top trace), LH (middle trace), and testosterone (bottom trace) in the vicinity of their respective sites of production. The three hormones are seen to exhibit the sort of fluctuations observed in the results of experiments. Note particularly the LHRH spikes and the exponential "sawtooth" form of the LH trace. The dotted lines on the LH and testosterone curves indicate the values of (respectively) $L$ and $T$ (see text).

Fig. 3). Here, the increase in pulse frequency and the elevation of the LH baseline level are due to the removal from equation (1) of the term in $T$.

Although clock-based models can accommodate the changes seen in the castrate, they do not actually predict them, since they lack any mechanism for the effect of testosterone.

A piece of corroborative evidence concerns the physiology of human males suffering from primary hypogonadism. The testes of these individuals release little testosterone, and the pattern of LH release resembles that in castrated monkeys (Matsumoto & Bremner, 1984; Winters & Troen, 1983). Testosterone infusion reasserts normal LH patterns both in hypogonadal men (Matsumoto & Bremner, 1984; Winters et al., 1979) and in castrated monkeys (Plant, 1982).

Data on hormone infusion into normal males are limited, but it appears that the infusion of testosterone leads to a decrease in LH pulse frequency (Santen, 1977).
This too is predicted by our model: equation (3) becomes

$$\dot{T}(t) = -d_{T} T(t) + r_{T} L(t - \tau_{p-T} - \tau_{0}) + k$$

(3')

where $k$ is the infusion rate, and the simulation then yields Fig. 4.

The effects of LHRH antagonists are to eliminate the pulsatile pattern of LH secretion and to bring LH levels down to low, constant (but non-zero) levels (Ellis et al., 1983). Although complete suppression of LHRH action at the pituitary would, according to our model, lead to zero levels of all three hormones, it is unlikely that these antagonists have such a complete effect. Residual LHRH action would be expected to stimulate low levels of LH production. Provided that the ensuing concentrations of LH and of testosterone are not sufficient to switch off hypothalamic secretion of LHRH, there will be no pulsatile behaviour, but rather continuous release. This behaviour is shown in Fig. 5.
There is less relevant data for LHRH: most of the experimental data relating to LHRH concentrations refer to female animals (e.g. Carmel et al., 1976; Clarke & Cummins, 1982; Sarkar et al., 1976). The only measurements made in males of which the authors are aware are those of Dluzen & Ramirez (1983). In their short abstract they claim that LHRH pulse frequency remains unchanged in castrated rats. Were this to be confirmed, it would necessitate a significant reappraisal of current thinking (see Lincoln et al., 1985).

One possible interaction that we have chosen not to include in our model is that between testosterone and the pituitary. There are two reasons for this omission, one empirical and one heuristic. Although the possibility of such an interaction has not been ruled out, it is considered that "the hypothalamus is a better candidate as a provider of the primary control" (Lincoln, 1979). Moreover, our model does not require that testosterone affect the pituitary in order to be in agreement with the data as discussed above.
Evidence concerning the effects of LH on the hypothalamus is scant. The only experiments of which we are aware which claim to argue against such a "short loop" effect are those of Gay (1974) and Carmel et al. (1976).

In Gay's experiments, the kidneys of intact and castrated adult rats were removed (Gay, 1974). One result of this was that blood levels of LH rose significantly in the castrates, but did not change in normal animals. However, blood samples were taken only at four-hourly intervals prior to the sacrifice of the animals at 24 hours after nephrectomy, so that the effects of pulsatility could not be observed. Furthermore, the effects of so drastic an event as nephrectomy are not limited to the retardation of LH excretion.

The second set of experiments involved the sectioning of the pituitary stalk in ovariectomized (female) monkeys (Carmel et al., 1976). The portal blood was collected from the severed pituitary stalk, and the concentration of LHRH (only) was sampled. The LHRH was found to exhibit pulsatile behaviour, and the authors
suggest that this was strong evidence against any significant pituitary effect on hypothalamic LHRH release.

The arguments against the significance of these results are several. First, the postoperative trauma would almost certainly influence the pattern of hormone secretion, particularly in the few hours that elapsed before the experiments were terminated. Secondly, the possibility of the leakage of portal blood cannot be discounted, since LHRH levels at the pituitary were not measured. Thirdly, the continued pulsatility of LHRH after pituitary stalk section could not be taken to mean that there is no pituitary effect, only that it cannot be the only effect. Fourthly, and crucially, the data from experiments performed on female animals cannot be used to constrain models for males. Finally, the pattern of LHRH pulses obtained is inconsistent not only with the model we propose but also with the various "clock" models. The interpulse intervals that Carmel et al. found in their animals were very variable—between one and three hours, which is much longer than the "clock" models would allow (Lincoln et al., 1985).

Given that the model here discussed provides an adequate description of the pattern of testosterone release in males, we are naturally led to ask whether a similar model can account for the pattern of oestrogen release in females. The situation in the female is more complicated, however, owing to the effects of the menstrual cycle. The control of the menstrual cycle involves hormones other than oestrogen, such as progesterone and FSH, and perhaps also other neural structures in the hypothalamus (Kalra & Kalra, 1983; Silverman et al., 1982). In addition, there is the significant effect of the "priming" of the pituitary by LHRH (Fink et al., 1976). Thus any adequate model of the female system would necessarily be more complicated than the one we have presented for males.

One further question that arises is whether the model we have constructed may be adapted to account for the changes in hormone patterns that occur at puberty. Before puberty, the hormones are present in low concentrations, and they do not show pulsatile behaviour. It is not until puberty that pulsatility becomes evident, and then primarily during sleep (Reiter & Grumbach, 1982).

The reasons for this behaviour are unclear. Hohlweg & Dohrn (1932) suggested that these changes reflect changes in the "sensitivity" of the brain's response to testosterone. Indeed, the pre-pubertal hormone patterns may be described by our model, by making suitable changes to the controlling parameters. Simply reducing $r_R$, for example, results in steady low levels for all three hormones, as in Fig. 5. (For the role of hypothalamic maturation at puberty, see Ojeda et al., 1980 and Reiter & Grumbach, 1982.) The nocturnal aspect of pubertal development may be associated with the secretion of melatonin by the pineal gland (Preslock, 1984; Reiter, 1980).

The analysis presented above has been applied to reproductive hormones, but there is, of course, no reason why similar descriptions should not be applicable to other hormone systems. Almost all classical hormones are known to exhibit pulsatile behaviour, but the mechanisms are obscure. It is also known that many endocrine systems involve two or more separate hormones, and thus are likely to involve some sort of "feedback" behaviour. While it is possible that such interactions are essen-
tially independent, it seems equally likely that feedback loops are often "nested" one within another, or otherwise connected in more complex networks.

Testing the Model

We have pointed out above that most of the features of our model have been supported independently by experimental evidence. The principal feature about the model which is still controversial is the "feedback" effect of LH on the hypothalamus. It is now considered likely by many that some pituitary factors have a direct influence on the hypothalamus, either through the blood-brain barrier or via "retrograde" transport in the portal system (e.g. Bergland & Page, 1978), and there is some evidence which suggests that LH has such an effect (Motta et al., 1969). Whether or not LH does indeed affect the hypothalamus in the way we suggest can be tested experimentally (on unanaesthetised animals). The procedure might be as follows.

(i) Simultaneous measurements of LHRH (in the portal system) and of LH and testosterone (in the bloodstream) are made.

(ii) The pituitary is then ablated. Changes in the levels of the three hormones are monitored.

According to our model, the pattern of hormone concentrations before pituitary ablation should resemble that shown in Fig. 2. After pituitary ablation, the bloodstream level of LH would naturally be expected to fall to zero, and following it the concentration of testosterone should also decay. With no LH or testosterone in the bloodstream, the hypothalamic secretion of LHRH should be continuous.

This is, unfortunately, an ambitious experiment to carry out. The only experiment of a similar nature of which we know was that performed by Carmel et al. (1976), which was discussed above.

Experiments might also show how the various relationships in the model should be "tuned" to account for such departures as the nonlinearity of the testis response. However, we believe that these changes would not alter significantly the predictions of the model. Further experiment might indicate how the model might be extended to allow for effects external to the LHRH/LH/testosterone system.

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