THE TRANSFER FUNCTION RELATING HYPOPHYSEAL RESPONSE TO HYPOGLYCEMIA IN MAN

J. C. HOWARD and D. R. YOUNG

Ames Research Center, NASA
Moffett Field, California 94035

ABSTRACT

Experiments have been undertaken to develop preliminary data regarding quantitative aspects of the control and regulation of the level of serum growth hormone. Responses measured in human test subjects during insulin induced hypoglycemia suggest that the pituitary gland behaves like a critically damped system. In order to provide information which would be useful in predicting hypophyseal response, a simplified mathematical model was formulated. Confirmation that the equations are valid in the region of the time domain considered strengthens our conviction that the model can be used to make predictions in the frequency domain. Since diseased or defective homeostatic mechanisms may impair the capability of the pituitary gland to control the secretions of growth hormone, open and closed loop transfer functions were obtained. Our analysis predicts that open loop conditions will result in hormonal oscillations, the nature of the oscillations depending on the values of the physiological sensitivities.

MATHEMATICAL MODEL

Two sets of experimental data that show the glandular response of human subjects to insulin induced hypoglycemia have been obtained.[1,2] One set shows the response of a group of healthy subjects while resting; the other shows the response of the same group of subjects while exercising. On the basis of the assumptions outlined, a mathematical model consisting of two first-order linear differential equations was formulated.[1,2] The equations are similar in form to those describing the glucose, insulin homeostasis problem.[3] They describe a single compartmental analysis of growth hormone, 'glucose interaction. When they are solved for the serum growth hormone concentration, a second-order differential equation is obtained.[1,2] This equation gives the hormonal response of the pituitary gland to a glucose forcing function. The solution requires that four sensitivity coefficients and two production rates be known. Since none of these coefficients is available at the present time, a solution was obtained by indirect methods. Depending on the relative magnitudes of the coefficients, the equation can describe an oscillatory hormonal response with various degrees of damping, or a nonoscillatory response which may be divergent, critically damped, or overdamped. Since the observed hormonal response displayed no oscillatory or divergent tendencies, it was concluded that the system was either critically damped or overdamped. Moreover, a critically damped response differs from an overdamped one in that the concentration level returns to its final or steady-state value in a shorter time. In view of these considerations, it was tentatively assumed that the physiological subsystem was critically damped. If the hypothesis of a critically damped system is adopted, it is possible to show that the hormonal response depends on only two parameters. Because one of these parameters represents a physiologic state and the other a physiologic invariant for the range of conditions considered, they are more meaningful than the individual sensitivities.

TRANSFER FUNCTION

According to Wiener, one of the tasks of physiological cybernetics is to disentangle and isolate the different parts of the complex of voluntary, homeostatic, and postural feedbacks.[4] A large group of cases in which some sort of feedback is not only exemplified in physiological phenomena but is absolutely essential for the continuation of life is found in what is known as homeostasis. The homeostatic feedbacks differ from the voluntary and postural feedbacks in one general way: they tend to be slower. Likewise, the typical effectors of homeostasis, the smooth muscles and glands, are slow in their action compared with the typical effectors of voluntary and postural activity.

According to the mathematical model, the output of the pituitary gland which is the homeostatic effector in the case under consideration is related to the glucose perturbation by the following transfer function:

$$H(s)/I(s) = [a_1 s/(s + a)^2] \quad (1)$$

If it is assumed that the pituitary gland is operating as a closed loop system, this equation is the closed loop transfer function. In this case, it is pertinent to ask: What is the corresponding open loop transfer function? The answer to this question is important because, with physiological control systems, defective or diseased controllers may produce an open loop situation. Moreover, if the response of the system is recognized as an open loop response, diagnosis is simplified and appropriate remedial action can be taken.

Let the open loop transfer function be denoted by X(s), then

$$X(s) = a_1 s/[s^2 + (2a - a_1)s + a^2] \quad (2)$$

Open-Loop Response:

If a diseased or defective controller were to produce an open loop situation, the response of the pituitary gland to a serum glucose deficiency would depend on the relative magnitudes of the system parameters. In the event that the parameters satisfy the following inequality

$$0 < a_1 < 2a \quad (3)$$

the glandular response would be oscillatory, with a frequency of oscillation of "a" radians per minute. A root locus plot would show that satisfaction of condition (3) assures that the oscillations are not divergent. Since the damping ratio is given by

$$\zeta = [1 - (a_1/2a)] \tag{4}$$

the effect of increasing a_1 is to decrease the damping ratio, while the frequency remains constant. Changes in the damping ratio are also induced by variations in the parameter "a." However, in this case, the frequency of oscillation is also changed. When physiological conditions are such that

$$0 < a_1 \ll 2a \tag{5}$$

the resulting oscillations would be heavily damped and would quickly die out. On the other hand, if conditions were such that

$$a_1 \doteqdot 2a \tag{6}$$

the hormonal oscillations would be very lightly damped and would tend to persist indefinitely. A condition such as

$$2a < a_1 < 4a \tag{7}$$

would lead to divergent oscillations. A nonoscillatory divergence would occur if

$$a_1 \geqslant 4a \tag{8}$$

The physiological parameters of the subjects used in this study satisfied condition (8). It would appear, therefore, that a failure of the pituitary feedback mechanism in otherwise healthy subjects would lead to an excessive secretion of growth hormone.

SUMMARY

The results of our computer studies suggest the following: (a) under conditions of rest as well as prolonged physical work, the sensitivity of serum growth hormone production to serum glucose concentration "a_1" is constant; (b) the parameter "a" which determines the growth and decay of the serum growth hormone response is larger in resting subjects than in exercising subjects. A preliminary study of the consequences of a failure of the feedback mechanism in otherwise healthy subjects reveals the influence of the physiological sensitivities involved. Although the sensitivity of serum growth hormone production to serum glucose concentration has no influence on the frequency of hormonal oscillations, it does affect the open loop damping ratio. As the sensitivity is increased the tendency of induced hormonal oscillations to decay is reduced. Furthermore, the analysis shows that the sensitivity of serum growth hormone production to serum growth hormone concentration and the sensitivity of serum glucose production to serum glucose concentration influence both the frequency of hormonal oscillations and the extent to which these oscillations are damped. More specifically, the effect of increasing either of these sensitivities is to ensure greater attenuation of hormonal oscillations. Moreover, in this case, the frequency of the oscillations would be increased. Conversely, a reduction in either of these sensitivities would cause the system to oscillate at a reduced frequency with less attenuation.

NOMENCLATURE

a	Combined sensitivity of growth hormone production to growth hormone concentration and glucose production to glucose concentration (1/min)
a_1	Sensitivity of growth hormone production to glucose concentration (1/min)
H	Growth hormone concentration (mμg/ml)
I	Time history of glucose perturbation (mg/ml)
s	Laplace transform exponent

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