Hypothesis

A metabolic switch produced by enzymically interconvertible forms of an enzyme

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A system of enzymically interconvertible enzyme forms (interconversion cycle) is known to increase the sensitivity to regulators. Here it is shown that this system may also provide a discrete switching mechanism in which the response is maintained when the stimulus is removed. These switches may be important in producing discontinuous metabolic changes such as those associated with cell differentiation.

Interconvertible form *Metabolic switch* *Metabolic control* *Irreversible response*

1. INTRODUCTION

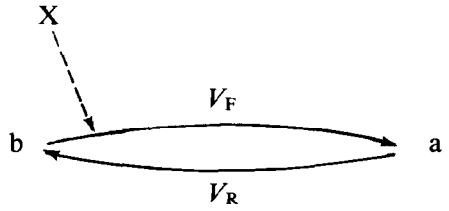
Most metabolic control systems must return to their initial values when the stimulus is removed. For example, in muscle the rates of the pathways supplying ATP for contraction must return to their resting values as soon as possible after activity ceases; otherwise ATP would be depleted and metabolism disrupted within a few seconds. Consequently, for most metabolic control systems the response of an enzyme activity to its regulator(s) is continuous and 'reversible'.

However, some systems can be switched from one state to another and then remain in the 'stimulated' state even after the stimulus is removed. Cell differentiation is one extreme example, but it is also observed with some metabolic systems: for example, the stimulatory effect of insulin on pyruvate dehydrogenase in adipocytes persists during subsequent fractionation of the tissue [1].

These and other examples indicate the existence of switching mechanisms which effectively 'lock' a system into a new state, i.e. the response to its regulator(s) is discontinuous. This may be the result of a 'physical' interaction; for example, the physical blocking of actinomyosin ATPase in resting muscle by tropomyosin (see [2]). However, such switching may also be provided by relatively simple enzyme kinetics, without the need for any physical organisation.

2. SWITCHING AT AN INTERCONVERSION CYCLE

Consider an enzyme which exists in 2 enzymically interconvertible forms, one active and the other inactive,



If V_F and V_R are simultaneously active this system constitutes an 'interconversion cycle' (see [3,4]), and regulator X, by altering the activity of V_F, changes the amount of enzyme in the active (a) form. If the 'reverse' reaction, V_R, follows hyperbolic (Michaelis-Menten) kinetics with respect to [a], so that

$$V_R = V_m[a]/(K_a + [a]),$$

and if V_R approaches saturation with [a], (i.e. [a]

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$\gg K_a$), small changes of [X] can produce extremely large changes of [a] [5,6]. Nevertheless, if the forward reaction, V_F, follows similar kinetics with respect to [b] (or indeed follows any kinetic response which gives just one value of V_F for each value of [b]), the initial [b]/[a] ratio is always restored when [X] returns to its initial value.

However, if the response of V_F to [b] is 'substrate-inhibited' as in fig.1, the response of the cycle may be very different. Let us assume that, initially, 95% of the enzyme is in the inactive (b) form, which corresponds to point 'x' on the kinetic response for V_F (fig.1). If [X], and hence V_F, is increased, there is a net conversion of b into a, so that [b] decreases. However, since [b] is on the 'right hand side' of the peak, this decreased [b] increases V_F and thus reinforces the effect of X. As long as [b] remains in region A of the curve the cycle can reach a new steady state in which most of the enzyme is still in the b form. However, if [b] decreases into region B it produces a much larger increase in V_F (which then decreases [b] to an even greater extent) until [b] enters region C: here V_F now decreases as [b] decreases and a new steady state is reached with very little of the enzyme in the b form, i.e. the enzyme is almost fully active.

If [X] now returns to its initial value, V_F decreases, less b is converted into a and [b] therefore increases. However, since [b] is in region C of the curve, the increased [b] increases V_F and produces a new steady state in which [b] is still very small: the rate of cycling returns to its initial value (V_C), but with [b] at point 'y' instead of x. Consequently, the enzyme remains locked in the active state even though the stimulus has been removed. To inactivate the enzyme, the value of [X], and hence V_F, must be decreased much further until [b] increases sufficiently to enter regions B and A of the response.

This type of response is simulated in fig.2 which shows that, as [X] increases from its initial value, X_0 (= 1), there is only a moderate activation of the enzyme until [X] reaches approx. 1.7 units: at this point (A) there is a large and virtually complete activation (point B) which is not reversed when [X] returns to its initial value (point C). Thus line AB

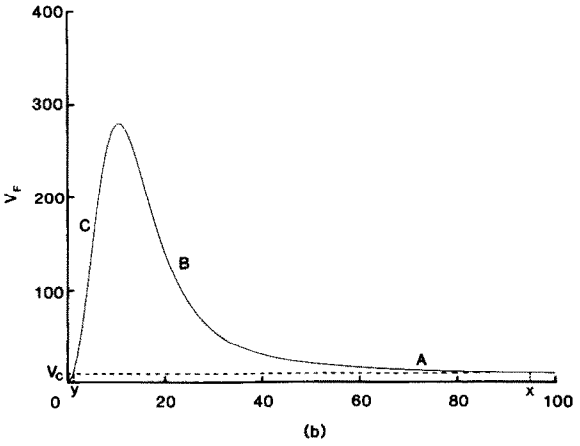

Fig.1. Substrate-inhibited response of V_F to [b]. V_C represents the initial rate of cycling for the response in fig.2. The curve is generated by the empirical equation, $V_F = A \cdot [X] \cdot [b]^s$, where $s = n \cdot K^m/(K^m + [b]^m)$. The values for n, m and K are 2, 2 and 20, respectively. To give the initial conditions required for fig.2 (i.e. [b] = 95 when V_C = 10 and [X] = X_0 = 1), A is set at 6.7. It should be emphasised that this equation is used to generate a suitable curve to model 'substrate inhibition', and the parameters n, m, K and A do not necessarily have any physiological significance.

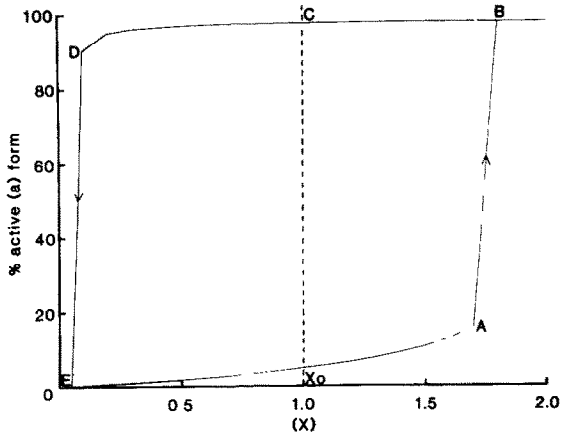

Fig.2. Metabolic switching at an interconversion cycle. The cycle is shown in the text. $V_R = 100 \cdot [a]/(10 + [a])$ and $V_F = 6.7 \cdot [X] \cdot [b]^s$, where $s = 2 \times 20^2/(20^2 + [b])$: see fig.1. The initial rate of cycling (when [X] = X_0 = 1) is 10 units. The system was solved numerically (at each value of X) using the equations:

$$[a]_n = [a]_{n-1} + \Delta t \cdot (V_F - V_R)_{n-1},$$

$$[b]_n = 100 - [a]_n,$$

with $\Delta t = 0.001$, until steady-state values of [a] and [b] were obtained. The response is 'reversible' between points zero and A and between B and D, but not between A and B or D and E (see text).

of fig.2 represents a unidirectional change: the response can proceed from A to B, but not from B to A, and this effectively switches the enzyme activity 'on'. To switch the activity 'off' [X] must be decreased to approx. 0.05 units, when there is an almost complete conversion into the b form (line DE). After this [X] must be increased to approx. 1.7 in order to switch the activity on again. Thus line DE also represents a unidirectional response, in the direction D to E, which effectively switches the activity off.

Consequently, this system can provide a relatively simple and effective switching device without the need for any 'physical' organisation. Indeed it could be made even more sensitive by choosing different values for the parameters in the rate equations. However, it is presented here as an essentially qualitative hypothesis, since there is as yet no evidence that it operates in any physiological control system. Nevertheless, interconversion cycles occur at many steps in metabolism [2,7] and substrate inhibition has been observed with several enzymes [8,9]. Therefore it is quite possible that this type of 'kinetic switch' has evolved to produce some of the discrete, as opposed to continuous, changes in enzyme activity that are characteristic of processes such as cell differentiation.

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