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BIPHASIC REGULATION IN LIGAND-RECEPTOR INTERACTIONS

MICHEL BOUNIAS

Laboratory of Biochemistry, University and INRA-Avignon, B.P. 91, F84140 Montfavet, France.

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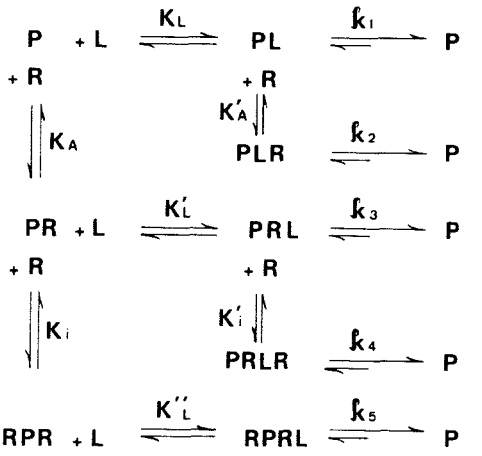
A model is examined in which an excess of activator may inhibit the response in a ligand-receptor interaction. The equation accounts for biphasic responses in which an effector stimulates the response at low concentrations and then inhibits the response at higher concentrations, towards a limit that can be higher, identical or lower than the initial value. Reciprocal features could be observed according to the values of the involved parameters. A maximum 7 dimensions can be found in the space of the parameters of the equation which is of the simple form: $v = (A + B + C).\ S^n/(H + S^n)$.

KEY WORDS: Ligand-receptor interactions, biphasic regulation.

INTRODUCTION

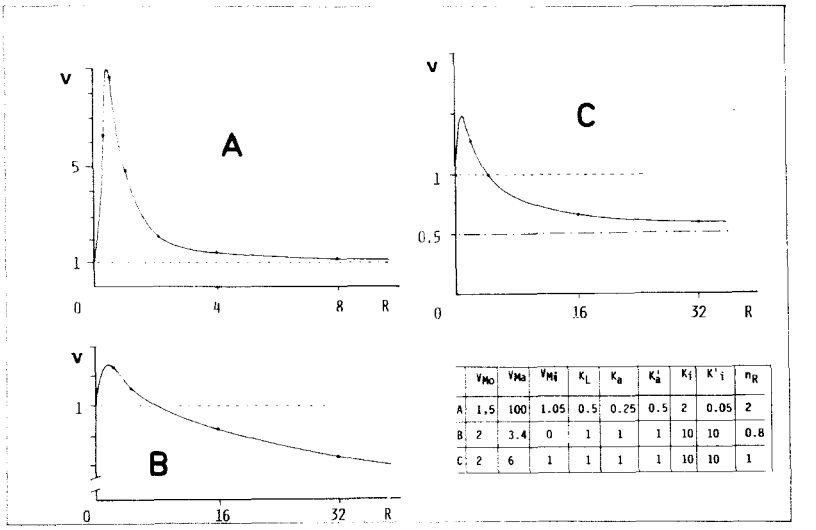
A biphasic regulation process occurs when a ligand acts on a receptor in two opposite ways according to its concentration. Although such cases have not been very often described, the most well known among these involve a first activation phase, at low ligand concentrations, followed by an inhibition phase at higher concentrations. Examples have been provided by the action of L-leucine on Barley leaves alkaline phosphatases[1] of phospholipids on brain synaptosome acetylcholinesterase[2] but also by hormonal interactions. In animals, somatostatin biphasically controls the glucagon stimulated glucose production of hepatoxytes[3], while in plants, cytokinins biphasically control the chlorophyll content of Cucumis sativus coytledons[4] and L-lactic acid biphasically acts on the growth of watercress[5]. Of course, these various examples correspond to direct molecular interactions in the first two cases, and to indirect effects in the others. However it can be expected, at least in some cases, that organismic effects such as chlorophyll content or growth might reflect the peripheric consequence of a corresponding underlying molecular interaction, as this was the case for L-leucine action on the photosynthetic apparatus of Barley leaves[1]. Probably due to the limited amount of experimental evidence, the equations of biphasic mechanisms have not been thoroughly considered. Some aspects have been pointed out by Shiner and Solaro[6] through a non-classical theory while the possibilities offered by the classical theory of mass action law (so far the strongest chemical basis) have just been suggested[7]. The aim of the present communication is therefore to express one of the likely simplest general equations and the various features that it is able to cover.



SCHEME 1 Molecular interactions involved in biphasic regulation. K_L etc are dissociation constants; k_1 etc are kinetic constants. P is product or/and response.

MODEL AND RESULTS

A ligand (L) (substrate or hormone) binds a receptor (P) (enzyme or hormonal receptor) giving an active complex (PL). The regulator (R) binds the complex (PL) and eventually the free receptor, leading to the possible ternary complexes (PLR) and (PRL). Lastly, these complexes in turn bind the regulator, leading to the quaternary complexes ($PRLR$) or ($RPRL$) (scheme 1). Let k_1, k_2, k_3, k_4, k_5 the kinetic constants of the respective responses of all five complexes and K_L K_a, K_a', K_i, K_i' the respective



	v_{No}	v_{Na}	v_{Ni}	K_L	K_a	K_a'	K_i	K'_i	n_R
A	1.5	100	1.05	0.5	0.25	0.5	2	0.05	2
B	2	3.4	0	1	1	1	10	10	0.8
C	2	6	1	1	1	1	10	10	1

FIGURE 1 Three types of biphasic curves obtained with the parameters given in arbitrary units. Asymptotic limits are: identical to initial level (A), zero (B) or lower than initial level i.e. 0.5 (C).

dissociation constants of (PL), (PR), (PLR), (RPR) and $(PRLR)$, and K_L', K_L'' those of (PRL) and $(RPRL)$. Then, assuming, for simplification, that $k_2 = k_3$ and $k_4 = k_5$ (or that (PLR) and $(PRLR) = (RPRL)$, the initial rates of the responses are:

$$v_o = -d(PL)/dt = k_1(PL) \tag{1}$$

$$v_a = -d(PLR)/dt = k_2(PLR) \tag{2}$$

$$v_i = -d(PRLR)/dt = k_4(PRLR) \tag{3}$$

Then defining the corresponding maximum responses $V_{Mo} = k_1(P_{tot})$, $V_{MA} = k_2(P_{tot})$, P_{tot} = sum of the molecular species containing (P), the representative equation of the resulting rate is:

$$V_R = 1/N \cdot L/(K_o + L) \cdot [V_{Mo} + (R/K_A')\, V_{MA} + (R^2/K_A' K_i')\, V_{Mi}] \tag{4}$$

$$\text{where } N = 1 + R/K_A' + R^2/K_A' K_i' \tag{4-1}$$

$$K_o = K_L\,|1 + (R/K_a)(1 + R/K_i)|/|1 + (R/K_a')(1 + R/K_i')| \tag{4-2}$$

It is noteworthy that when $K_a = K_a'$, $K_i = K_i'$, then $K_o = K_L$.

Lastly, (L) and (R) can affect the respective Hill coefficients n_L and n_R, possibly $\neq 1$.

The limits of v_R are the following:

$$\text{For } R \to 0,\ v_R \to v_o = V_{Mo} \cdot L/(K_L + L) \tag{5-1}$$

For $R \to \infty$, $v_R \to v_\infty = V_{Mi} \cdot L/(K_L \cdot K_a' \cdot K_i'/K_a \cdot K_i + L)$ that is, since $K_a'/K_a = K_L'/K_L$ and $K_i'/K_i = K_L''/K_L$, $\lim. v_R\,(R \to \infty) = V_{Mi} \cdot L/(K_L'' + L)$

(5-2)

The corresponding limits of K_o may be noted: For $R \to 0$: $K_o \to k_L$. For $R \to \infty$: $K_o \to K_L''$.

The model can be representative of an activation at low doses ($k_2 > k_1$) followed by an inhibition at higher doses ($k_4 < k_1$) towards a limit that can be $v_\infty = 0$ ($k_4 = 0$), $v_\infty = v_o$ ($k_4 \neq 0$ and $V_{Mi}/V_{Mo} = (K_L'' + L)/(K_L + L)$), or $v_\infty \gtrless v_o$ ($k_4 \neq 0$ and v_∞ as in equation (5-2)).

Examples are illustrated in Figure 1. It should be emphasized that symmetrical features, i.e. inhibition at low ligand doses followed be reactivation at higher doses, can be accounted for using the same model, but assuming $k_2 < k_1$, $k_4 > k_1$.

The described model represents a simple extension of the Botts and Morales[8] scheme and can be considered, because of its simplicity, as one of the simplest, and thus of the most likely models accounting for biphasic responses. However, the parameters space contains as many as 7 independent dimensions in the more general case, including the resulting Hill coefficient n_R, so that a topologic study is needed in order to search for a rational way of calculating the various involved parameters.

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