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The influence of the baseline on the size of pharmacological responses: a theoretical model

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It is frequently observed that the size of the response to a given dose of an agonist changes if a shift in the baseline activity of the test system occurs (e.g. Trendelenburg, 1974). A theoretical model is presented which describes how the position of the baseline may influence the relationship between biological stimulus (Stephenson, 1956) and effect (Figure 1).

Situation 1

Let us assume that agonist A is a full agonist which needs to activate all the receptors to produce its maximum effect (E_{1max}), i.e. there are no spare receptors in the system. In this case $E_1 = S_1$ (where E_1 is the effect and S_1 is the stimulus in the presence of a given concentration of A). Let us further assume that $E_{1max} = r_1$ (where r_1 is the possible range of effect within the system).

Situation 2

Let us assume that the baseline is shifted over a range a, and thus the range of observable effect is reduced ($r_2 = r_1 - a$). In this situation $S_{2max} > E_{2max}$, indicating the presence of functionally spare receptors in the system. Let us further assume that the shift in the baseline was due to a given concentration of drug B which acts at separate, but functionally synergistic receptors compared to the receptors activated by drug A. Thus the equation suggested by Ariëns, Simonis & van Rossum (1964) to describe functional synergism is applicable:

$$Q = E_1 + a - E_1 \frac{a}{E_{1max}} \qquad (1)$$

where Q is the effect in Situation 2 measured from the baseline in Situation 1. Using the baseline in Situation 2 as a basis of reference:

$$Q = E_2 - a \qquad (2)$$

$$E_1 = S_1 = S_2 \qquad (3)$$

$$a = S_{2max} - E_{2max} \qquad (4)$$

Substituting Q from eq. (2), E_1 from eq. (3) and a from eq. (4), eq. (1) becomes

$$E_2 = S_2 - S_2 \frac{S_{2max} - E_{2max}}{S_{2max}} \qquad (5)$$

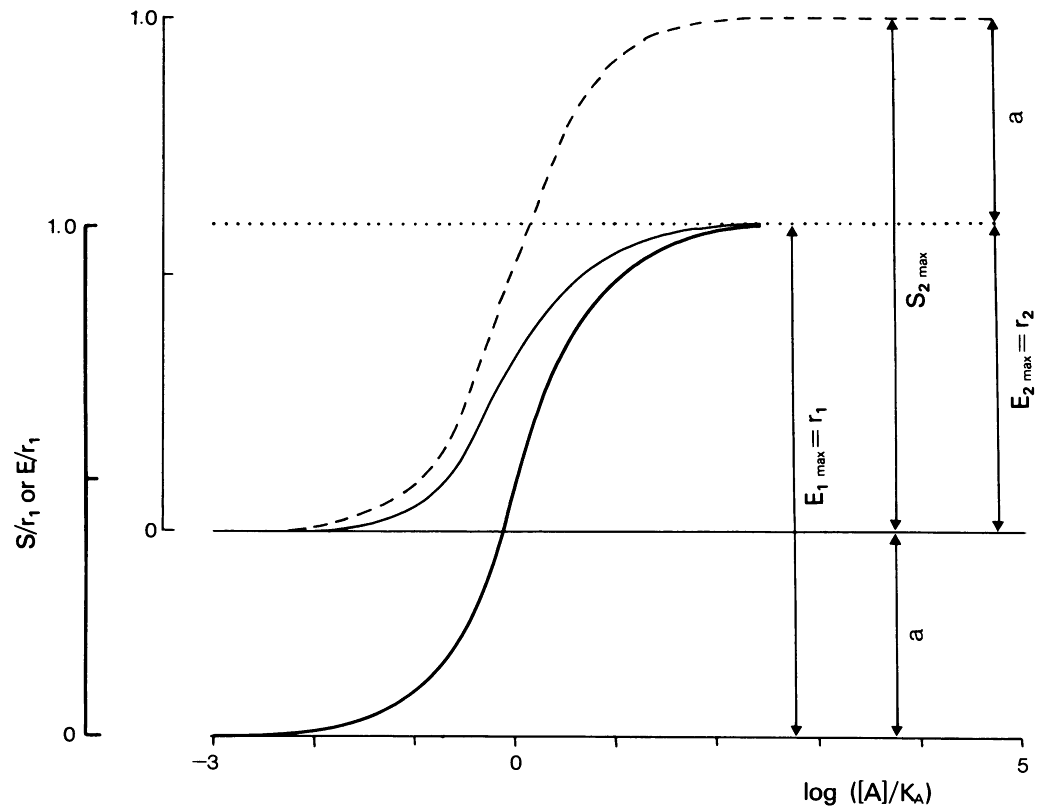

Figure 1 Theoretical concentration-stimulus and concentration-effect curves showing two positions of the baseline activity of the system (Situations 1 and 2). Abscissae: logarithm of the concentration of the agonist ([A]) expressed as a proportion of the dissociation constant of the agonist-receptor complex (K_A) ordinates: sizes of stimuli and effects expressed as proportions of the range of observable effect in Situation 1 (r_1). Thick solid line: concentration-stimulus and concentration-effect curves in Situation 1; broken line; concentration-stimulus curve in Situation 2; thin solid line: concentration-effect curve in Situation 2; dotted line: level of maximum observable effect within the system.

In a more general form, the relationship between stimulus and effect will be:

$$E = S - S\,\frac{S_{max} - E_{max}}{S_{max}} \qquad (6)$$

The model suggests that the value of $S_{max} - E_{max}$ can be altered by a change in the position of the baseline, and this in turn will change the absolute size of any submaximal response to the agonist.

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